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ORIGINAL ARTICLES

RESULTS OF DEEP ROENTGEN-RAY TREATMENT IN 258 CASES OF MALIGNANT TUMORS.

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NEW YORK.

(From the Memorial Hospital, New York City.)

During the past four years we have had the opportunity of study-ing the action of roentgen rays with and without other adjuvant methods in a series of 658 cases of malignant tumors and allied con-ditions referred to the roentgen department of the Memorial Hos-pital. In summarizing these results, and as a basis for this paper, we have selected 258 cases in all of which the microscopic diagnosis and clinical data were established beyond question. Outside of the cases of Hodgkin's disease it will be seen that the cases treated repre-sent what is commonly recognized as true cancer, and therefore the study of these cases will serve to indicate what results we can logically expect to attain in treating this class of cases with the roentgen rays at the present time. *No endeavor has been made to feature the few cases that responded unusually well to treatment,* and we have elim-inated from our lists all cases in which the diagnosis was not verified by competent microscopic examination, all cases in which the clinical data and subsequent histories were incomplete, and cases that discontinued treatment, etc.; also all cases of uterine carcinoma as they will be reported by the gynecological department. The cases were classified as follows:

EPITHELIAL TISSUE.

	Total.	Improved.	Unimproved.	P. I.—S. D.	Improved; still under treatment.	Dead.
1. Basal-cell epithelioma	16	16	0	0	16	0
2. Squamous-cell epithelioma	38	5	33	4	1	37
3. Alveolar and scirrhus carcinoma of breast	59	32	27	18	14	45
4. Carcinoma of testis (teratoid)	5	5	..	3	..	5
5. " of neck (branchial clefts)	7	..	7	..	..	7
6. " of esophagus	1	..	1	..	..	1
7. " of stomach	2	..	2	..	..	2
8. " of intestines (carcinosis)	4	..	4	..	..	4
9. " of colon	4	1	3	1	..	4
10. " of rectum	7	..	7	..	..	7
11. " of thyroid	5	4	2	3	1	5
12. " of lung	3	1	2	1	..	3
13. " of tonsil	1	..	1	..	..	1
14. " of ovary	2	1	1	..	1	1
15. " of larynx	6	..	6	..	..	6
16. " of gall-bladder	1	1	..	1	..	1
17. Melanoma	4	1	3	1	..	4

CONNECTIVE TISSUE.

	Total.	Improved.	Unimproved.	P. I.—S. D.	Improved; still under treatment.	Dead.
18. Sarcoma, mixed, myeloid, spindle, etc.	38	6	32	4	2	36
19. Sarcoma, melano	4	1	3	1	..	4

LYMPHATIC TISSUE.

	Total.	Improved.	Unimproved.	P. I.—S. D.	Improved; still under treatment.	Dead.
20. Sarcoma, lympho	21	15	6	8	7	14
21. Pseudo leukemia	12	10	2	3	7	5
22. Lymphatic leukemia, chronic	4	3	1	2	1	2
23. Splenomyelogenous leukemia	2	2	..	2	..	2
24. Lymphoma	1	1	..	1		
25. Thymoma	1	1	..	..	1	

OTHER TISSUES.

	Total.	Improved.	Unimproved.	P. I.—S. D.	Improved; still under treatment.	Dead.
26. Mixed tumors (parotid)	1	..	1	..	..	1
27. Endothelioma	1	..	1	..	..	1
28. Glioma retina	1	..	1			
29. Lipoma recurrent	1	1				
30. Rhabdomyo sarcoma	1	..	1	..	..	1
31. Hypernephroma	1	.:	1	..	..	1
32. Adamantenoma	1	..	1			
33. Embryonal carcinoma	2	1	..	1	1	1
	258	108	150	54	54	203

EXPLANATION OF CLASSIFICATION. In most of our cases "improved" means a diminution in the size of the lesions, with a diminution of the symptoms. If the lesions were ulcerative in character there were evidences of healing best shown in early cases of basal-cell epithelioma, in which the healing was uniformly prompt, progressive, and complete, except in late and very extensive lesions. If the lesions were subcutaneous or metastatic, "improved" means that they diminish in size.

Pain was very strikingly relieved in many of the cases; discharge diminished in quantity and odor. If the patient's symptoms improved, but the lesions did not show improvement, the case was not considered improved.

"Unimproved" means that the patient's lesions or symptoms or both were not improved and that the lesions steadily progressed despite treatment.

Some of the cases showed such marked improvement under treatment at first that although they subsequently died it was deemed important to call attention to this class of cases by tabulating them under the heading of "primarily improved, subsequently died." Our experience has led us to expect certain cases to do very well under treatment at first and raise great hopes of recovery in the patient and the therapeutist. Such cases have frequently been reported in the literature during this stage of improvement, and not uncommonly the patients have relapsed and died by the time the reports have been published. Some cases are improved but still under treatment, so that their ultimate results are not known. These are classified in the column "improved, still under treatment."

APPARATUS AND TECHNIC. The apparatus and technic used in administrating the roentgen-ray dosage consists of a high-tension transformer capable of giving sparks 10 inches long between the poles of the spark gap, while the Coolidge tube is in operation (this high-tension transformer is run by the 220 volt alternating current) broad focussed Coolidge tubes regulated so as to back up a 10-inch parallel spark gap while in operation and passing 7 milliampères of current through the tube. The focus skin distance was 6 to 8 inches, the rays were filtered through 3 mm. of aluminum in the early treatments and through 4 mm. of aluminum later in the series. The dosage was measured on the skin by means of Corbett's modification of the Lovibund tintometer. Our average skin dose is 3 B Saborcaud, equivalent to 15 Holtzknecht or 30 Kienbock units to each area treated. The average time required to obtain this dose was 3 to 4 minutes.

The roentgen rays were applied through portals varying from 3 to 5 cm. square, using the cross-fire method of traversing the diseased tissues at many angles. The maximum dose for skin toleration was administered as shown by the tintometer readings and verified by the erythemas produced. The dosage was never repeated over a given area at intervals of less than two weeks. We found that we could treat 2 to 3 portals at a sitting without causing nausea in our patients, but treating a greater number of portals always caused depression and nausea even when the patients were under alkaline treatment to overcome acidosis. When treating directly over the stomach the patients were prone to become extremely nauseated. To illustrate the number of portals used, let us take for example a

case of carcinoma of the breast, in which we would select the following portals:

Anterior chest, 2 to 4 portals.
Posterior chest, 2 to 4 portals.
Axilla and axillary line, 1 to 2 portals.
Supraclavicular fossa and neck, 1 to 2 portals.
Total, 6 to 12 portals over each side of the thorax.

In selected cases both mammary regions were treated through these multiple portals. Attempts were made to increase the skin dosage tolerance by various methods of dehematizing the skin
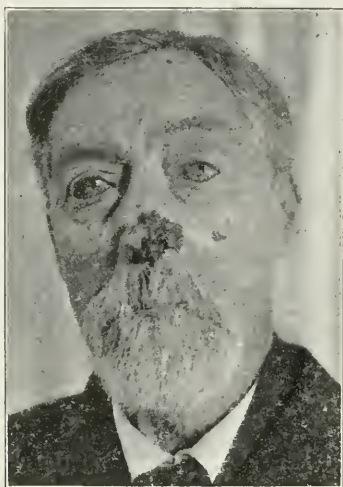
FIG. 1.—Before treatment.   FIG. 2.—After treatment.
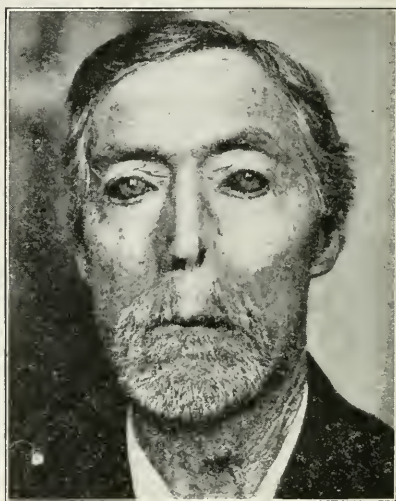
FIGS. 1 and 2.—Microscopic diagnosis: basal epithelioma. Duration, fourteen year . Previous treatments: local applications of ointments, pastes, caustics, curettement, high-frequency current, etc. Occupation: farmer. Preëpithelial keratoses are scattered over face, neck, and hands. Two treatments improved the patient so much that he discontinued treatments for seven months, believing himself well. On his return it required seven more treatments over the nose to control the condition and eight treatments to clear the face, neck, and hands of the keratoses.

through pressure, ice-bags, and adrenalin injections, but without sufficient success to make us feel warranted in continuing them. Attempts were also made to increase the number of secondary rays generated in the tumors by injecting suspensions of heavy metals and also by producing hyperemia within the tumors. These attempts were not attended with any noteworthy success. The application of heat by diathermy in conjunction with the roentgen rays was tried, and it appears to be a synergist to the roentgen-ray treatment in superficial cases and in those cases in which the heat acted practically as a removal by cautery. When sloughing obtained, however, in these cases the wounds were sluggish in healing.

INTERPRETATION OF THE THERAPEUTIC RESULTS. *Basal-cell Epithelioma.* Except in old advanced cases the results in this type of lesion are uniformly good, all 16 cases responding promptly, the lesions healing in from three to twelve weeks, and with one exception have remained well to date. With proper microscopic diagnosis other more painful methods are unnecessary.

Squamous-cell Epithelioma. The bad results in this class of cases are in marked contrast to the good results obtained in basal-cell epithelioma. The one improved case shown in the table of cases was treated with the roentgen rays combined with diathermic coagulation. He was symptomatically well for six months and then showed signs of local recurrence. He was again treated with massive doses of roentgen rays locally and roentgen rays cross-fired through the cervical lymph nodes. The condition seems to be under control at the present time, but the prognosis is dubious. This is a good illustration of the course of squamous epithelioma under treatment.

Carcinoma of the Breast. A majority of these cases show a primary improvement evidenced by diminution in the size of the tumors, both primary and metastatic, with frequent disappearance of the latter. Diminution in pain, discharge and fetor are also notable. Metastases are always more amenable to roentgen therapy than primary growths, and the earlier they are treated after their appearance the more evident this becomes. Efficient treatment of early metastases may cause a complete clinical disappearance of cancer tissue. In cases in which the therapeutic effect of the ray has not entirely succeeded, careful search will usually reveal small groups of viable cells, accounting thereby for such local recurrences as do occur. Besides the primary lethal effect of the ray on the malignant cells we have to do in all probability with a second and very important factor in determining the success or failure of our method of treatment. That is the degree in which the stroma has gone in supplying the necessary circulation for the cells of the growth, for where these cells have time to be provided with abundant stroma, containing a rich blood supply, it seems more difficult to eradicate the cancer cells entirely. It is for this reason, we believe, that metastases are more influenced than primary growths and why early metastases can be obliterated entirely. We believe that the greatest emphasis should be laid on the value of the preoperative and postoperative raying in all cases, in which surgical removal is contemplated, because the surgeon can never feel assured that he has not left behind isolated cells. And if these cells are to be attacked successfully, the time to do it is, we believe, when they are not connected organically with the circulation of the host.

Lymphosarcoma. This class of cases gives us our most brilliant primary results. In many cases the tumors melt away and there is a notable restoration of health and sense of well-being. Unfortu-

nately in our experience they all relapse and the process proceeds despite all treatment.

Lymphoid Group. In pseudoleukemia, chronic lymphatic leukemia, splenomyelogenous leukemia, lymphoma we see the same result as in lymphosarcoma; primary improvement with disappearance of the tumors is the rule. Ultimately these cases relapse and die. In thymoma, however, we have had good results which have lasted to date. What the ultimate result will be we cannot at present state, but in this one group we are optimistic.
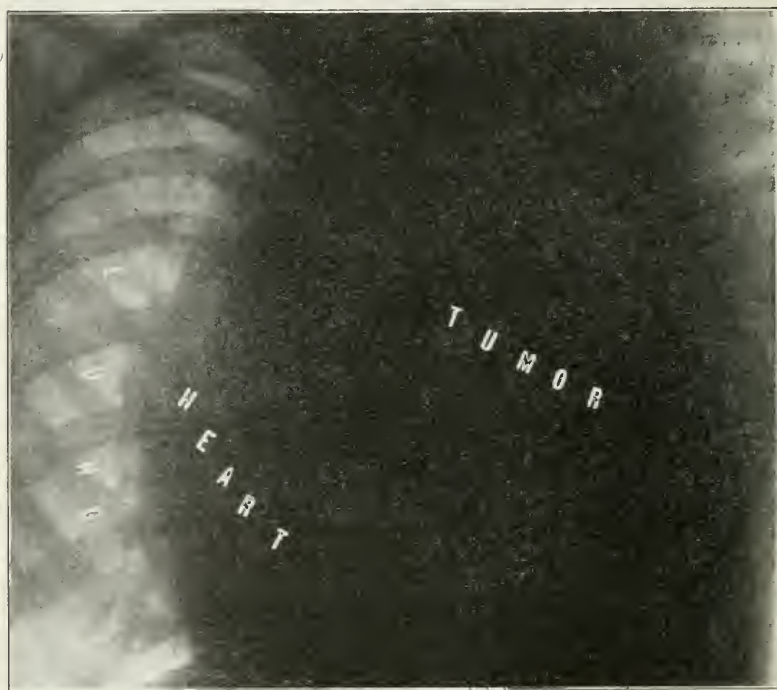
FIG. 3.—Embryonal carcinoma of the left lung before treatment, January 12, 1915.

Carcinoma of the Viscera. All failed to show noteworthy improvement except carcinoma of the thyroid and adenocarcinoma of the ovary. One case of large inoperable adenocarcinoma of the ovary involving the omentum and viscera was given three times our maximum dose of roentgen rays through an open wound and in the abdomen. All evidences of the tumor disappeared subsequent to this for a period of nine months. The patient then returned to the hospital in a feeble condition with evidence of widespread pelvic adhesions. She was given as much roentgen-ray treatment as her feeble condition warranted. She finally died in a very much emaciated condition and with symptoms of obstruction of the bowels. At autopsy there were no evidence of any carcinoma in the pelvis

whatever; all had disappeared and been replaced by connective tissue. There were extensive metastases in the liver and spleen.

Embryonal Carcinoma. In our series we had 2 cases of embryonal carcinoma. They showed very marked initial improvement. One relapsed despite all treatment; the other is still in the initial improvement stage.
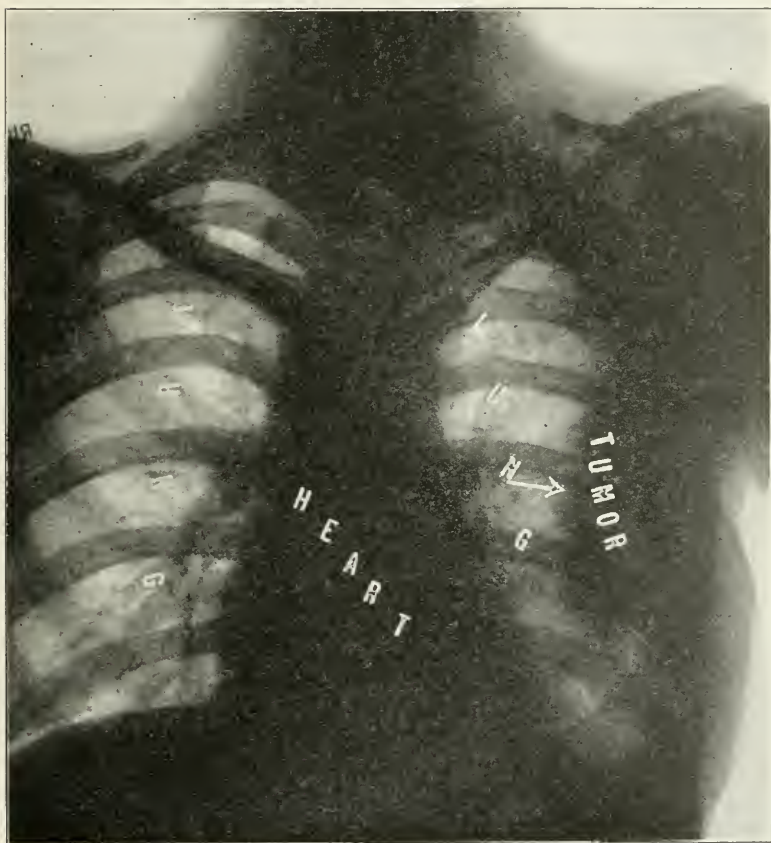
Fig. 4.—Embryonal carcinoma of left lung after treatment, May 14, 1915.

THERAPEUTIC RESULTS BASED ON PHYSIOLOGICAL ACTION OF THE ROENTGEN RAYS. The improvements obtained in certain classes of cases are such as might be expected when one considers the physiological action of the roentgen ray.[1] [22] It has been shown that the deep tissues of the body which are most susceptible to roentgen rays are the lymphoid tissues of the spleen, lymph glands and follicles, thymus gland, the spermatogenous epithelium of the testis, the Graafian follicles of the ovary, endothelial cells, embryonal cells, and the nucleus of cells, especially those in an active state of division,

Based on these physiological actions it is logical to expect that we would find the greatest therapeutic effects of the roentgen rays in diseases causing lymphatic, testicular, and ovarian tumors and tumors made up of embryonal cells, and this is borne out in experience as we get most effect in lymphosarcoma, the leukemias, embryonal carcinoma, carcinoma testis of teratoid origin, and adeno-carcinoma of the ovary. In this series of cases we were fortunate in being able to observe 33 cases of lymphosarcoma and 18 cases of Hodgkin's disease. These cases will be published in detail subsequently.

CONCLUSIONS. From a study of these cases we are justified in drawing the following conclusions in regard to the value of roentgen rays in cancer:

1. Roentgen rays give excellent therapeutic results in basal-cell epithelioma.

2. They ameliorate cases of carcinoma of the breast, ovary, and testis, tumors lymphatic structures especially when these tumors are made up of cells of an embryonal type.

3. While we cannot successfully maintain that the roentgen rays have yet proved to be a cure in cancer it is worthy of note that these rays as well as those of radium applied with removal when possible produce more uniform improvements in cancer than any other agents heretofore known, and the use of these agents in cancer is established until some effectual constitutional treatment for cancer is found.

4. Pending the discovery of some effectual constitutional treatment every effort should be made to increase the ameliorating effects of the radio-active methods.

5. Surgery should not ignore the benefits of these methods in the treatment of cancer, particularly in the postoperative raying and treatment against metastases.

6. Most of our improved cases eventually relapsed, and while their lives were prolonged and made more comfortable by the roentgen-ray treatment they eventually died of the disease.

7. In some instances these ameliorating effects were very striking and deserve particular attention in the hope that we may eventually discover means of making these ameliorations more lasting and even permanent.

CASE HISTORIES. *Results of Deep Roentgen-ray Treatments in* 258 *Cases of Malignant Tumors.*

CASE II.—Mrs. Mc. K.; aged forty-five years.

Microscopic Diagnosis. Alveolar carcinoma breast.

Chief Complaint. Recurrent tumors of breast and enlarged glands above the clavicle.

Family History. One grandparent, mother, and one sister had cancers.

Personal History. Patient was operated on for ectopic gestation in 1907. Had a hysterectomy for myoma in 1910.

Present Illness.   Onset in November, 1913, with the appearance of two nodules in the right breast.   No pain.   Nutrition good.

December, 1912.   Radical amputation of right breast and dissection of axillary glands.   (Dr. C. H. Peck, Roosevelt Hospital.)

Pathological Report.   "Section of the tumor mass is composed entirely of epithelial cells, packed away together and lobulated, with dense fibrous connective-tissue bands containing numerous small round cells, a few polynuclears, moderately congested bloodvessels, and some fat.   The fibrous stroma is slight, the cellular elements predominating.   Mitoses are present.   Section of the smaller mass shows groups of these cells having the same characteristics invading the breast tissue.   Section from the axillary glands shows a thickened capsule and trabeculæ rather densely infiltrated with small round cells and containing a few congested bloodvessels, and the lymphoid tissue is almost entirely replaced by invading groups of epithelial cells having the same general characteristics as the original tumor.   Mitoses are numerous."   (Baldwin Mann, pathologist.)

Received postoperative roentgen-ray treatments for one month.

March, 1913.   Recurrences developed along the healed scar. Enlarged glands appeared above the clavicle and in the epigastric region.

November 10.   Massive deep roentgen therapy begun, treatments being administered to all sides of the chest, axillæ, and neck. 510 X (Kienboch) units being administered with water-cooled tubes and 1290 X (Kienboch) units being administered with Coolidge tubes.   Total 1800 X (Kienboch) units.   One persistent nodule in the scar about 4 cm. long was treated with radium, total 98 millecurie hours (Dr. H. H. Janeway) filtered through 1 mm. of lead administered in eight treatments.   Under this treatment all nodules disappeared and the patient was symptom-free until October 20, 1915 (a period of nearly two years).   At this time she complained of pain in her back (lumbar region).   Roentgen-ray examination showed no evidence of bone metastases.   The pain was very much relieved by roentgen treatments.

December, 1915.   Patient developed general metastases all over her body.   Large masses appeared in the left breast, which was enormous and had a hog-skin appearance.   The left axilla was involved. Pain developed in chest and back.   The patient was evidently progressing into a stage of general carcinosis.   On account of the fact that the gamma rays of radium are more penetrating than the hardest roentgen rays generated from a Coolidge tube it was decided to use large quantities of radium emanations, heavily filtered, under Dr. H. H. Janeway's direction.   Between January, 1915, and July, 1916, she received a total of 51,908 millecurie hours of radium, using distance and various metal filters.   Under this treatment the tumors diminished very greatly in size and changed from edematous swollen masses to hard contracted masses.   The left breast became adherent

to the chest wall.   The patient's symptoms were greatly improved for a time; later she gradually failed, but is still alive at the present time.

The important points in this case are the strong family history of cancer; the well-developed and excellent nutrition of the patient, the development of a malignant type of cancer of the breast, as shown by its clinical course and morphology.   The radical operation within one month of the appearance of the tumor by a very competent surgeon under ideal hospital conditions; the recurrence of the growth with palpable supraclavicular and epigastric metastases within four months after the operation, rendering her in a condition hopeless for further operative intervention; complete relief of symptoms and palpable evidences of disease under roentgen-ray and radium treatment for two years subsequent to the development of this hopeless condition; after which she developed a condition of carcinosis which was ameliorated by enormous doses of radium emanation.   The analgesic and alterative actions of roentgen rays and radium.   The patient is still alive four years subsequent to the onset of her original disease and three years eight months after the development of hopeless metastases.

CASE III.—C. S., male; aged forty years.

Microscopic Diagnosis.   Lymphosarcoma.

Chief Complaint.   Recurrence of tumor of face on the left side.

Duration.   Ten years.

Family and Personal History.   Negative.

Present Illness.   Began ten years ago with the appearance of a nodule on left side of face close to the ear.   He was operated on several times.   A year ago the patient was treated with mixed toxins. The tumor retrogressed.   The patient continued to be treated with toxins while at home, but with no permanent improvement.

Physical Examination.   The patient is a well-nourished man in middle adult life, who has a tumor of the left side of the face.   His jaw is limited in motion, so that the teeth can only be parted one-third inch.   His tonsils and pharynx we were unable to examine. There is facial paralysis of the left side of the face.   The region of the left ear and all its surroundings show a hard prominence, which is red, and especially so behind the ear.   The external canal of the ear presents an ulcerated area covered with a purulent discharge. The scars of previous operations are seen beginning from the lobe of the ear and ending about $3\frac{1}{2}$ inches below.   The lymph nodes are not enlarged.   The abdomen is soft and no masses felt.   No edema of the legs.   Patient had been under treatment with mixed toxins for a period of about two years, but the growth did not diminish any so it was then decided to add roentgen-ray treatments.

November 20, 1913.   Roentgen-ray treatments were begun, and in all he received seven massive treatments.   After the third treatment (December 15) the tumor began to retrogress very markedly

and by the end of January, 1914, the entire mass was gone.   Patient left the hospital in a fairly good condition.   The growth did not recur.   The patient died six months later from nephritis.

Carcinoma Testis of Teratoid Origin.   This class of cases also gives us uniform initial improvement, followed by ultimate relapses.   In our series we had 5 cases; all improved; all died.

CASE IV.—Male; aged twenty-nine years.

Microscopic Diagnosis.   Carcinoma testis of teratoid origin with abdominal metastases.

Chief Complaint.   Tumors in abdomen particularly in the splenic region.

Personal and Family History.   Negative.

February, 1914, he first noticed an enlargement of the left testicle. In March this tumor was removed and the patient was symptom-free until July, when he had a sudden onset of abdominal pain, and on examination a tumor mass was discovered in the left lower abdominal quadrant.   The patient was then treated until March, 1915, by Dr. J. W. Vaughn's (Detroit) serum method, under which the tumor grew smaller for a time, but subsequently relapsed.

Physical Examination.   A well-nourished young man with no evidence of poor health except a hard mass in the left side of the epigastrium about the size of an orange.   Its outline is regular and it lies for the most part under the left rectus muscle.   It is not tender on deep palpation.   Liver is not enlarged.   No ascites.   Lymph nodes in groin slightly enlarged.   Wassermann reaction negative. He was placed on several special treatments by Dr. S. P. Beebe, without any apparent change in the patient's condition.

March 19 he was given a treatment over the abdominal tumor, after which it was noticeably diminished in size.   The treatments were repeated over the enlarged glands in the groin, after which they disappeared.   The special treatments were continued and the roentgen-ray treatments stopped, followed by prompt recurrences of the enlarged glands in the groin.   Roentgen-ray treatments were resumed at the patient's request and the tumors again disappeared.

May 29.   Roentgen-ray examination of the chest showed metastases in the hila of both lungs.   The patient received a total of 21 massive roentgen treatments over the abdominal, inguinal, and mediastinal lymph nodes.   These enlargements were all reduced under this treatment and were held in abeyance up to July, when the patient discontinued treatment.   The tumor masses subsequently recurred and the patient died of exhaustion.

Summary.   Case of carcinoma testis of teratoid origin.   Primary tumor removed within a month of the onset.   Metastases developed within four months after operation.   The generalized metastases were treated eight months by Vaughn's serum method, with primary improvement and subsequent relapse, he was then treated by a combination of special treatments, including autolysin and roentgen-

ray treatments covering a period of five months; it was noticeable that the size of the tumor diminished after each roentgen-ray treatment and at times were made to disappear and when the roentgen rays were omitted the tumors promptly reappeared; it is therefore logical to assume that the ameliorations were due directly to the roentgen-ray treatments. The patient subsequently died of exhaustion. This was the first case of this class of tumor which we had treated and before we knew of the efficacy of roentgen rays.

CASE V.—E. W.: female; aged seventeen years. Admitted to Memorial Hospital, January 10, 1915.

Chief Complaint. Swelling on the left side of the chest. Shortness of breath.

Present History. Six months ago (July, 1914) the patient began to have sharp pains around her heart, in the left axilla, and in her back. The pain lasted only a few seconds at a time. About the same time she became short of breath. She could not walk a block without resting two or three times. Six weeks ago she first noticed a small swelling near the left axilla. The swelling has increased in size very little since she first noticed it. Now she occasionally has pain in the swelling in her back. She has had several nightsweats. No cough. Has expectorated a small amount of whitish material. Nose bleeds occasionally. December 26 she was tapped, 1500 c.c. of fluid being obtained. She was admitted to the Jewish Hospital two weeks ago and was tapped again one week ago, 1500 c.c. being obtained.

Past History. Two years ago she had a cough which lasted a month.

Family History. Negative.

Physical Examination. The patient is a moderately well-developed and well-nourished girl, aged seventeen years. Mucous membranes rather pale. Skin normal. On the left side of the thorax, in the anterior axillary line, just below the lower edge of the pectoralis major muscle and partially covered by that muscle, there is a hard mass 10 cm. in diameter. The mass is circular in shape, has a smooth surface, and is firmly fixed to the chest wall. Skin over the mass normal in appearance and movable. Left chest appears larger than the right. Intercostal spaces on the left side bulging. Left chest immobile on respiration. Right chest moves normally.

Palpation. Tactile fremitus present on the right side and absent on the left side.

Percussion. Flatness over the whole left chest, both anterior and posterior. Normal resonance on right side.

Auscultation. Breath sounds distant over the whole left chest. Somewhat tubular in character in the lower part. On the right side breath sounds are normal. No rales or friction sounds heard.

Heart. Apex beat cannot be seen or palpated. On percussion the cardiac dulness extends one inch to the right of the sternum. Left

border of heart not made out. Heart sounds indistinct, except at the right border of the sternum. Regular and of good quality. Pulse rate 90 and of good force.

Abdomen. No masses, tenderness, or rigidity. Liver cannot be palpated. On percussion the liver dulness extends almost to the umbilicus. Spleen and kidneys cannot be palpated.

Summary. A moderately well-nourished girl, aged seventeen years. Hard, movable tumor, on anterior chest wall at the lower border of the left pectoralis major muscle. Flatness over the whole left chest with distant breath sounds. Heart displaced to the right. Liver enlarged. Palpable lymph nodes in groins. Roentgen-ray examination shows that the entire left side of the thorax is filled with a mass of tumor tissue with some effusion. Chest aspirated. 1000 c.c. of bloody fluid obtained. Tissue was removed under local anesthesia, on which the following pathological report was made:

"Tumor of axilla. The tumor is a malignant growth composed of small round and polyhedral cells. The structure is peculiar. There are many small arterioles with thickened or hyaline walls to which are attached the small tumor cells, as in perithelioma. Between these units are diffuse masses of tumor cells. The tumor cells resemble lymphocytes, but show a polyhedral tendency which suggests an epithelial or endothelial origin. There are many mitoses. The tumor may be a lymphosarcoma, or a malignant embryonal growth from some glandular organ."

Massive roentgen-ray treatments were begun, followed by noticeable improvement within ten days. The treatments were continued and the external tumor disappeared. Roentgen-ray examination showed pronounced diminution in the size of the intrathoracic tumor. Heart returned to its normal position. Lung relations on the right side have resumed their normal place. Patient discharged to the out-patient department February 27.

Condition. General health has improved. She has gained weight during the past three weeks. Still complains of sharp pains in the lower part of the left chest.

Physical Examination. Mass in left axilla almost disappeared. Moderate resonance over anterior and posterior part of left chest. Impaired resonance in left axilla and at base of lung. Breath sounds normal except over the dull areas where they are not heard distinctly. No rales or friction sounds heard. Heart seems to be in normal condition. Patient's condition continued to improve and she became symptom-free, remaining so until September 10, when she was readmitted because of shortness of breath. Roentgen-ray examination of the chest showed the tumor growing rapidly. Her general condition became gradually weaker and dulness developed over the entire left chest. Cardiac impulse displaced to right of sternum in the third interspace. Abdomen distended and tympan-

itic, and there was apparent paralysis of both legs.   November 13 the patient died.   No autopsy was permitted.

Summary: Duration: Fourteen months previous to treatment. Microscopic diagnosis: embryonal carcinoma of the chest of unknown origin. (A type of tumor which is unique in medical literature.)   A large tumor mass almost filled the left chest.   A hard movable tumor mass presented on chest wall.   No metastases demonstrable.   Marked dyspnea.   Patient received 28 massive roentgen treatments (840X) between January 22, 1915, and August 1, 1915, during which time she became symptom-free and 'much improved in health   The external tumor disappeared; the intrathoracic tumor diminished as shown in the illustrations.   One month later the patient's symptoms suddenly returned and progressed despite all forms of treatment.   Patient died of exhaustion.

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SYPHILITIC AORTITIS.[1]

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The development of internal lesions in latent syphilis is attended by such vague indefinite clinical manifestations as to render diagnosis

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during their incipiency often a matter of extreme difficulty. This obscurity of early signs and symptoms characterizes aortitis, and previous to the introduction of the Wassermann test and the employment of roentgen diagnostic technic, the lesion usually came to light only when it had advanced to the production of gross and often obvious mechanical manifestations. On account of its usual prolonged latency it was described according to the classification formerly in vogue as a form of so-called parasyphilis, the occasional case that pursued an active rapid course hardly sufficing to disturb this rating. As a parasyphilitic manifestation, aortic syphilis remained more or less separated in interest from the parent disease, and the role assigned to it being that of a late nutritive secondary it was viewed with comparative indifference. The isolation of spirochetes in the tunics of diseased aortæ and accumulated studies with the Wassermann test have in recent years combined to endow aortic syphilis with new significance, revealing the lesion in its proper light as true syphilis subject to all the activities and amenable to the same therapeutic attack as other forms of internal syphilis. Although pathologists describe fairly acute inflammatory changes at the root of the aorta in certain acute infections, notably rheumatism, these occur almost always in association with endocarditis, and, moreover, manifest a tendency to spontaneous subsidence very different from the progressive character of the aortitis of syphilis. These transitory non-specific types of aortitis are very little familiar to the clinician, so much so that it may be said, speaking clinically, there is but one form of aortitis, the syphilitic.

The Wassermann test has materially altered our views regarding the specific nature of aortic lesions. A positive Wassermann reaction has been obtained in over 80 per cent. of cases that showed characteristic aortic changes at autopsy, Eich's statistics showing 81.8 per cent. and Pearce's 78.5 per cent. Citron used the Wassermann test in all chronic cases of aortic regurgitation and found it positive in 60 per cent. Collins and Sachs tested 13 cases of aortic valvular disease finding the Wassermann positive in 11. By way of contrast they record an equal number of cases of purely mitral disease, similarly tested, with Wassermann positive in but 2 instances. Still more direct evidence of the syphilitic nature of aortic disease has been furnished by the isolation of the spirochete of syphilis in the tunics of diseased aortæ, such a finding being now of common occurrence. Moreover, the fact that lesions practically the same as syphilitic aortitis in the acquired disease have been found to exist in a high percentage of infants with congenital syphilis affords strong support to the claim that the lesion in adults is due to syphilis.

Syphilitic aortitis before it involves the valves is often latent. After it has produced aortic valve incompetency its progress is rapid, often bringing life to an end within two or three years.

Aortic regurgitations of syphilitic origin do very badly probably because of the association of deformed valves and constricted coronary orifices. The prognosis is far more serious than in cases of rheumatic origin even when of equal degree, compensation being less well established and the aorta more dilated.

Early in the course of aortic syphilis the involvement of a limited portion of the artery may appear of slight immediate significance. Its progression involves the risk of serious damage with, it may be, dilatation or aneurysm angina pectoris or most commonly aortic regurgitation. To detect this insidious lesion before it has advanced to the production of mechanical secondaries is consequently of great importance. Clinical recognition of the disease in its earliest stages gains greatly in importance from the fact that it may be treated by intensive antisyphilitic methods with some prospect of control. The diagnosis is often extremely difficult, since limited and circumscribed changes in the ascending portion of the aorta without involvement of the valve ring are seldom accompanied by clearly defined symptoms or signs. The greatest difficulty is encountered in individuals not recognized as being syphilitic. It is often the case for aortitis to be the only manifestation of the disease in otherwise latent syphilis, and one may expect in a considerable percentage of cases to encounter a completely negative history of syphilis. In one-half of Benary's cases and in 28.9 per cent. of Symmer's autopsy material, aortitis was the only manifestation of the disease detected at autopsy. The majority of patients coming under clinical recognition for aortic syphilis are in middle life, and experienced clinicians understand the significance of angina pectoris and aortic regurgitation originating in the adult.

Our most valuable aids in the diagnosis of obscure aortic disease are the Wassermann test and roentgen-ray examination.

It is now generally conceded that a positive Wassermann reaction means active syphilis somewhere in the body. From the frequency with which syphilitic arotitis is found accidentally at autopsy (according to Eich 42.8 per cent. of cases) we may assume that the infection may be harbored in that part of the vascular system for years without detection; indeed, it might even appear that the aorta is one of the main situations in which the infection may lurk in latent syphilis. A persistent Wassermann reaction in an otherwise latent case may consequently direct suspicion toward the aorta and a roentgen-ray study of this area should be made. The absence of a definite or confessed history of syphilitic infection should not be allowed to divert attention from such a possibility. This is especially important in women in whom historical data on this point are, for obvious reasons, obscure and unreliable. A negative blood Wassermann in a known syphilitic should not be accepted as inconsistent with a possible aortic lesion. Progressive aortitis may exist, although the blood has been Wassermann nega-

tive for years. The luetin test of Noguchi may occasionally reveal the disease when the Wassermann reaction is negative, as in certain cases presently to be related. Bearing in mind this frequency of aortitis in latent lues it is well that we should consider the possibility of a syphilitic etiology in any case of cardiovascular degeneration of obscure origin. If serological studies confirm this suspicion the aorta should be carefully examined by means of modern roentgenray technic.

The symptoms of syphilis of the aorta are pain in and about the precordium, dyspnea, hoarseness, paroxysmal cough, tachycardia, arrhythmia, general weakness and lassitude, and, under certain circumstances, elevated blood-pressure. These symptoms are seldom clearly defined during the period of early development of the disease. Various clinical criteria, such as the shape of the heart to percussion, peculiarities of rhythm, the paroxysmal nature of cardiac symptoms have been proposed to identify syphilitic aortitis. One need not emphasize the unreliability of such data.

There are certain physical signs which may be elicited by examination in most well-developed cases, but they are not of such a character as to especially indicate aortic syphilis. Among the most significant of these signs are a roughening or impurity of the first aortic sound and a sharp ringing aortic second tone, which if the aorta is much dilated may have a bell-like quality. Extension upward of percussion dulness over the sternum may exist, and there may be abnormal pulsation in the carotids and subclavian with an impulse in the episternal notch. None of these signs are, however, sufficiently characteristic to furnish grounds for diagnosis of syphilitic aortitis, since they are frequently noted in aortic atheroma and high blood-pressure states not connected with syphilis.

The primary aortic involvement is a small cell or granulomatous infiltration of the tunica media (mesaortitis) along the course of the vasovasorum. Eventually all three of the main coats of the aorta become affected the intima by secondary proliferative thickening. Coagulation necrosis, and subsequent connective-tissue changes lead to slow but extensive damage to the vessel wall, so that fairly characteristic gross appearances become established. Although maximum involvement appears to fall upon the first part of the arch and the ascending aorta probably because of the greater functional strain to which this portion of the vessel is subjected, no section throughout the vessel is exempt from attack. The involved areas appear as more or less well-defined elevated patches, the surface of the larger areas being often extremely irregular, with pittings, scars, and puckerings, making what Allbutt describes as "knotty masses" in the vessel wall (Fig. 1).

When secondary changes are extensive they are characterized not by calcification, as in arteriosclerosis, but by a gradual corrosion or thinning by scar formation, so that the vessel wall may become

translucent at points and there may be tiny aneurysmal bulgings or possibly a true saccular aneurysm. Frequently cellular infiltration about the mouths of the branches of the arch may cause distinct narrowing of innominate and left carotid or more or less occlusion of the coronaries.

In the earlier stages the vessel is perhaps but little dilated or deformed. If viewed from without little change may be noted (Fig. 2). It is on the inner surface of the artery that the changes appear (Fig. 3). The tendency of the disease in development is to spread to the aortic valve and by a general periarteritis in the cusps and between them the semilunar valve flaps become thickened and deformed, giving rise to valve incompetency. It is a common

Fig. 1.—Syphilitic aortitis with diffusely dilated vessel.   (From Pathological Museum, Rush Medical College.)

and important clinical observation that the aorta may be gravely affected, although the peripheral arteries apparently remain normal, and Brooks has emphasized the fact that the coronaries are apt to show a degree of involvement out of all proportion to general arterial change. It is the seat of the disease in the suprasigmoid portion of the aortic arch that threatens the integrity of the coronaries, and the steady progression of the disease accounts for the aortic valve defects aneurysm and anginas which constitute the morbid end-products of syphilitic aortitis.

Of all the methods of diagnosis to determine the presence of aortic disease, the roentgen ray is the most valuable. By its aid we may detect slight changes in the caliber and shape of the vessel

which entirely elude the methods of physical examination. Both fluoroscopic inspection and plate studies should be employed, the

Fig. 2.—Syphilitic aortitis; outer surface of vessel.

Fig. 3.—Syphilitic aortitis; inner surface of vessel. (From Pathological Museum of Rush Medical College.)

former for preliminary observation and the detection of abnormal pulsation and the latter to secure definite outlines and measurements.

The various roentgen-ray plates herewith reproduced were taken in the standing position, with a few seconds' exposure, and focal distance of seven feet, which provides for practically parallel rays and obviates distortion of the shadow.

The shadow of the normal aorta in the roentgenogram (Fig. 4) lies in its first portion behind the sternum and does not project beyond the right auricular curve. At the arch where it curves backward and to the left there appears a more or less well-rounded knob seen to the left of the sternum well above and distinct from the cardiac shadow. This aortic knob is not equally well defined in all normal aortæ. In the asthenic or dropped heart type it may hardly show at all, whereas in occasional cardiac roentgenograms it may be so prominent a feature as to be mistaken for aneurysmal bulging.
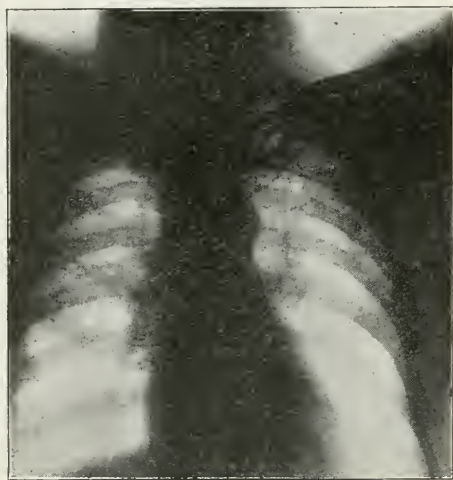
Fig. 4.—Normal aortic shadow.

It varies in prominence according to age, being less defined in early life than in adults, and in the aged and arteriosclerotic individuals the shadow may be sharply outlined and intensified from sclerous thickening and lime deposits (Fig. 5). It is less apt to be prominent in adult females than in males of corresponding age.

In aortitis the roentgen ray reveals two kinds of changes, i. e., alterations in density of shadow and changes in contour. In early aortitis the pathological process is almost invariably confined to the very origin of the aorta. As the vessel is not at this stage thickened and no lime deposits exist there may be merely a slight dilatation of the first part of the arch with exaggerated pulsation at that point. Wessler points out that some dilatation of the aorta is a very common finding in routine cardiac roentgenography, so that little special significance attaches to it. It is practically con-

stant in ordinary sclerosis of the aorta and in high blood-pressure states. In non-specific aortic sclerosis, however, it is nearly always accompanied by a prominence of the whole arch, and if blood-pressure be elevated by hypertrophy of the left ventricle.

In early cases of aortitis the heart is rarely enlarged unless there is coexisting valve defect or hypertension. Of course, aortitis and atheroma may be combined in the same case, when computation will be rendered difficult. With the progress of aortitis the artery becomes more and more dilated, and, as a result, the aortic shadow as it ascends from the heart is widened so that it projects beyond the shadow of the curved right auricle. In most instances the shadow is regular, but it may show slight bulgings or protrusion.

Fig. 5.—Non-specific aortic sclerosis. Note lime deposits at aortic knob.

Should the aortic dilatation extend to the arch the knob as it curves to the left may lose its well-defined curve, becoming flattened and broadened. Longcope has described a type of case in which the aortic shadow appears as a more or less truncated cone, with rounded apex and broad base resting on and fusing with the cardiac shadow. In any well-developed instance there may appear above the aortic shadow a pyramid-shaped shadow with base upward and beneath the clavicles. This seems to represent the dilated great arteries as they arise from the arch (Fig. 6).

While in the earlier stages of aortitis roentgen evidence may consist merely of a slightly increased curvature and pulsation at the aortic ampulla, a gradual dilatation and lengthening of the vessel supervene with further progress of the disease. These changes

combine to broaden and elevate the aortic shadow, and there occurs
in most cases some enlargement in the size of the heart whether
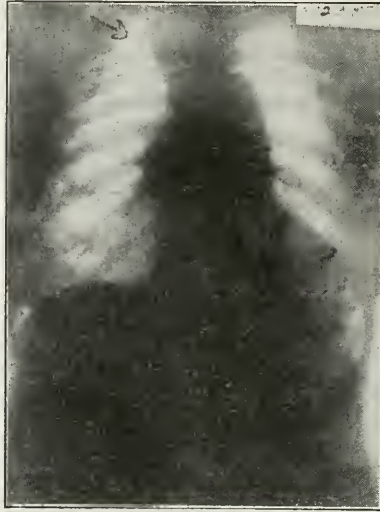
Fig. 6.—Advanced syphilitic aortitis with aortic valve insufficiency.   Marked
dilatation of aortic arch and great vessels as they arise from arch.
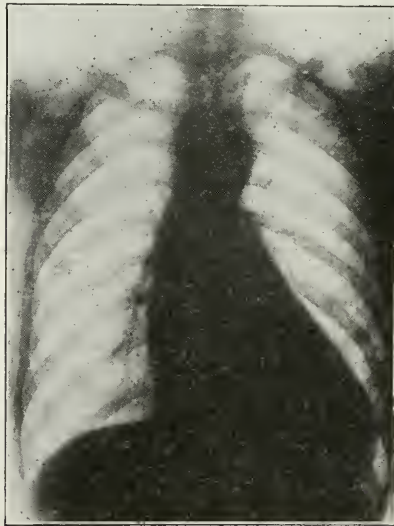
Fig. 7.—Non-syphilitic aortic insufficiency illustrating "aortic configuration" of
heart shadow

aortic insufficiency be present or not.   The increase in cardiac
diameters affects to a much greater degree the long diameter than

the broad diameter of the heart, the organ assuming a position more nearly horizontal than normal, producing a heart shadow somewhat boot-shaped, the heart lying low on the diaphragm. This type of heart shadow is very similar to that seen in high blood-pressure states (nephritis), although the marked pulsation of the left ventricle seen in hypertension is less manifest. This type of heart might be termed the aortic heart (aortic configuration) (Fig. 7) in contradistinction to the broad, rather round, or bag-shaped heart of mitral disease ("mitral configuration") (Fig. 8). With the spread of the disease to the aortic valve and the production of aortic insufficiency we find the heart shadow much augmented and its horizontal configuration correspondingly magnified. In advanced cases with superadded relative mitral insufficiency both
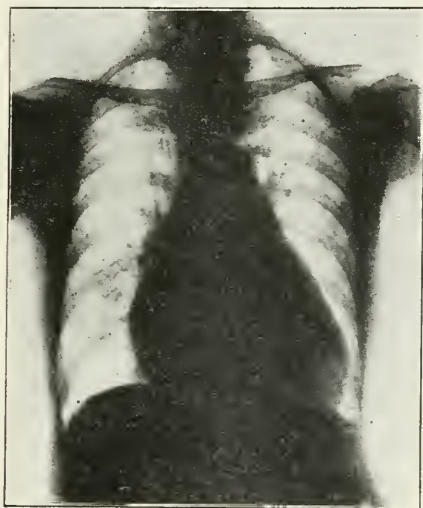
Fig. 8.—Mitral disease illustrating "mitral configuration" of heart shadow.

broad and long diameters are increased, combining to produce a very bulky heart shadow, the true cor bovis (Fig. 9).

It is obvious that until there is some dilatation, thickening, alteration of curve, or abnormal pulsation in the vessel, roentgen diagnosis of aortic disease is impossible. In consequence of this fact the roentgen ray cannot be relied upon for its detection in the early stage before mechanical defects begin to make their appearance. Clinical considerations and the Wassermann test must establish the diagnosis at this stage. An illustrative case may be cited.

CASE I.—A colored waiter, aged twenty-one years, complained of persistent aching pain in the left shoulder of two months' duration. This was accompanied by a recurrent substernal soreness, palpi-

tation, and a dry paroxysmal cough. He gave a history of chancre
two years previous to consultation. On examination an appreciable
enlargement of the heart could be made out, and along the left
border of the sternum a faint diastolic whiff was heard. Firm pres-
sure over the manubrium sterni caused a deep-seated aching
soreness. Blood Wassermann positive. Blood-pressure systolic,
155; diastolic, 85; pulse-pressure, 70. The roentgen ray beyond
some enlargement of the heart failed to reveal anything of
significance.

The clinical diagnosis was manifestly aortitis of rather active
type, yet at a stage too early for stretching of the aorta or other
mechanical defect to appear upon the roentgen-ray plate.
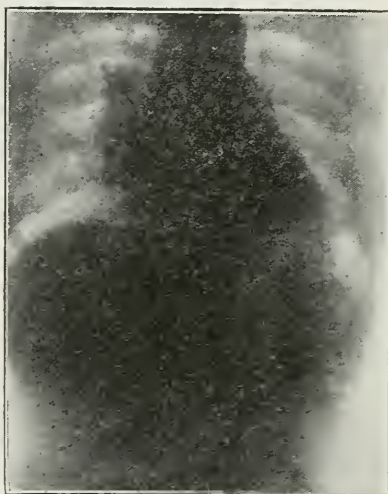
Fig. 9.—Extreme cardiac effects of aortic syphilis, i. e., aortic regurgitation,
relative mitral insufficiency, pulmonary hypostasis. This patient is alive, two years
after this plate was taken.

In contrast to this type of case may be cited the following instance
in which the roentgen ray confirmed and established beyond doubt
the clinical diagnosis.

CASE II.—A white man, aged forty years; widower; one child;
complaint: hoarseness, cough on exertion, dyspnea. Acknowledges
luetic infection ten years previous to consultation, for which he
received almost continuous treatment for four years. Blood Wasser-
mann, typically positive. Physical examination showed a somewhat
enlarged heart, with a ringing second aortic tone. The pulse was
regular. Blood-pressure: systolic, 140; diastolic, 100; pulse-pres-
sure, 40.

The roentgenogram (Fig. 10) showed typical aortic configuration
of the heart, with bulging of the first part of the ascending aorta.

The following example of well-developed syphilitic aortitis possesses points of unusual interest:

CASE III.—Single white man, aged forty years; complaint, palpitation and irregular heart action, lack of endurance, lassitude, and depression. Gave a history of lues at age of twenty-nine, with continuous treatment for two years. For three years previous to consultation blood Wassermann tests have been made at regular six-month intervals, with invariable negative reports. The last Wassermann test was taken six months before roentgenogram was made and proved negative.
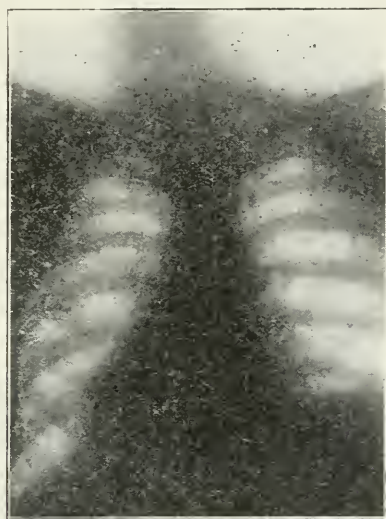
FIG. 10.—Case II.   Heart shadow displays aortic configuration with bulging of first portion of ascending aorta.

Physical examination revealed an enlarged heart, aortic systolic murmur, accented second aortic tone, premature contraction arrhythmia. Blood-pressure: systolic, 210; diastolic, 150. Early tabetic signs. The urine contained albumin and casts. Renal function index with the 'phthalein test 60 per cent. Clinical diagnosis: syphilitic myocarditis, nephritis. The roentgenogram showed a typical aortic type of heart and stretched aorta.

The points of particular clinical interest in this case are the existence of extensive and probably progressive cardiovascular lesions of syphilitic type in an individual who for several years had been Wassermann negative, and was led to consider himself cured of his syphilis. The extent of damage already wrought by the cardiovascular disease would appear to indicate that it was of some years' standing.

The peculiar lassitude and depression which was the chief complaint of this patient is a symptom interpreted by Allbutt as significant of coronary involvement. A point of interest to be noted in this case is the association of aortic disease with signs of early tabes. This is an association frequently noted in the literature. In manifest tabes, Stadler found aortic disease in almost all cases. He regarded so-called cardiac crises as being in reality angina pectoris due to coronary stenosis. Strümpell emphasized the frequent association of aortic syphilis and tabes and statistics from various sources attest its frequence. In general, symptoms of aortic disease appear later than the earliest tabetic manifestations. This is perhaps not because aortitis is a later development but rather that it has a longer latency than tabes.

The cases thus far briefly described represent aortic disease in a relatively early stage of its development. Progress of the lesion inevitably tends to impair the integrity of the aortic valve producing as a result insufficiency of the valve apparatus. How soon this mechanical secondary comes to pass depends more upon the activity of the process than upon its duration. No estimate can be given of the average period required for the production of valvular defects, although, generally speaking, it is certainly not an early development. Occasionally valvular disease is seen to develop early and run a rapid fatal course, as in the following instance:
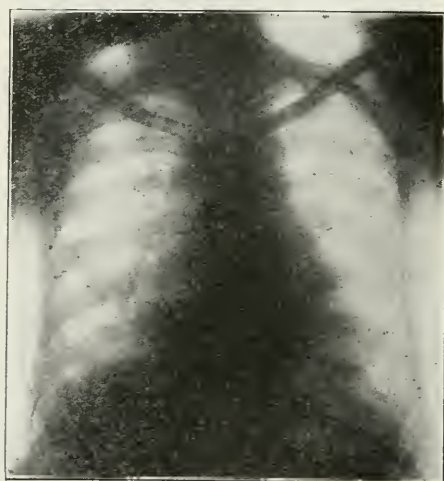
Fig. 11.—Case IV. Aortic and cardiac dilatation.

CASE IV.—Colored porter, aged twenty-five years; complaint, severe dyspnea, precordial pains. Duration of symptoms, six weeks; advent sudden; previous health considered good until development of foregoing symptoms. Luetic infection at age of

twenty; no active antisyphilitic treatment. Blood Wassermann strongly positive. Clinical diagnosis: aortic insufficiency, relative mitral insufficiency, pulmonary hypostasis. Termination, death after one week in hospital seven weeks after development of cardiac symptoms. Roentgenogram (Fig. 11) was taken eighteen hours before death and shows a greatly enlarged heart increased in both long and broad diameters. The aortic shadow is increased in breadth and elevated reaching as high as the sternoclavicular angle. This case illustrates how rapid may be the cardiac disorganization produced by aortitis, death resulting in this case five years after the initial syphilitic sore.

Aortic disease was formerly looked upon as a late development in syphilis. While, generally speaking, and especially in a clinical sense, this may perhaps be true, it is by no means always so. Along with other cases reported in recent contributions (Brooks, Longcope) the foregoing clinical history serves to discount the claim that aortic disease has a long latency and slow progression.

The following case represents an interesting variant of the usual clinical course of aortic disease:
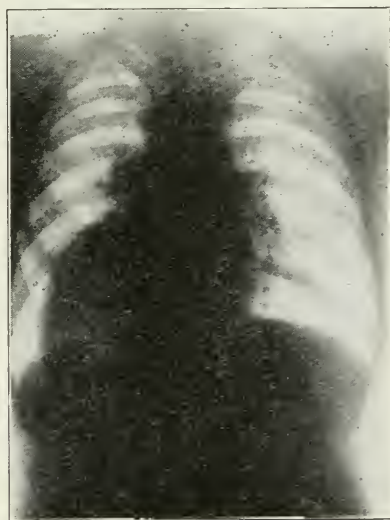
Fig. 12.—Case V. Anterior front view. Increase in both long and broad diameters; dilated aorta.

Case V.—A white engineer, aged thirty-two years; married; two children, one healthy, one, dead at three weeks, "had a patent foramen ovale." Syphilis denied. Complaint: dyspnea, cough, tachycardia. Duration of symptoms three months; advent sudden, following exertion at high altitude. Urine contains albumin and casts. Renal function index, 50 per cent. Blood-pressure: systolic,

200; diastolic, 80; pulse-pressure, 120; blood Wassermann, strongly
positive. Clinical diagnosis: aortic insufficiency, mitral insufficiency,
nephritis. Roentgenogram (Fig. 12) shows the heart shadow
increased in both length and breadth from the combined aortic and
mitral incompetency. The shadow of the aorta is widened and
rises high in the chest. Another semilateral roentgen exposure
(Fig. 13) shows this well and indicates beautifully the enormous
thickness of the heart shadow.

The duration of this patient's syphilis must rest on assumption
and may perhaps be estimated as less than seven years (the age of
his healthy child) and more than four (the date of birth of the
congenitally defective child). The development of nephritis may
by increasing aortic and cardiac strain have served to hasten the
progress of the aortic disease.

FIG. 13.—Case V.   Semilateral view.

CASE VI.—Colored cook, aged thirty-six years; complaint:
dyspnea, chronic cough, orthopnea, slight edema. Duration of
symptoms, six months. Previous health good. Syphilis denied.
Blood Wassermann, strongly positive. Clinical diagnosis, aortic
regurgitation. Roentgenogram showed aortic configuration in-
crease in cardiac diameter 32 per cent. This case is a typical one
of progressive syphilitic aortitis in latent syphilis and demon-
strates how silent may be the progress of the vascular lesion until
grave valvular secondaries arise. The liability of the colored race
to cardiovascular syphilis is notorious and need not be emphasized
here.

Syphilitic aortitis may exist in individuals who fail to react to
the Wassermann test, as is shown in the following case:

CASE VII.—Hebrew peddler, aged forty-nine years; married; three children; complaint: pains in body, dyspnea, cough, general weakness. Duration of symptoms, one year. Syphilis denied. Blood and spinal fluid Wassermann negative. Luetin test typically positive. Roentgenogram (Fig. 14) shows heart to be of aortic configuration; *type asthenique;* dilated and lengthened aorta. Increase in cardiac diameter 10 per cent.

FIG. 14.—Case VII. Increase in cardiac diameter 10 per cent. Heart is of aortic configuration; asthenic or dropped heart type.

This with the following case illustrate that a negative Wassermann both blood and spinal fluid tests should not be taken as indubitably disproving a syphilitic etiology for aortic disease. The luetin test of Noguchi may reveal the disease and supply the necessary diagnostic link.

CASE VIII.—Colored housemaid, aged thirty-eight years; widow; complaint: orthopnea, chronic productive cough, no edema. Duration of dyspnea one week, cough chronic for three years. Syphilis denied. Blood and spinal fluid Wassermann both negative. Luetin test typical pustular reaction. Roentgenogram shows heart to be of aortic shape; costal-phrenic angle not clear on plate; dilated aorta. Increase of cardiac diameter 20 per cent.

During residence in hospital patient had six typical attacks of angina pectoris, the paroxysms being relieved by nitrites. Intensive treatment with neosalvarsan and mercury brought about great subjective improvement. Three months after leaving hospital there had been no recurrence of angina paroxysms.

The following 2 cases represent slightly different aspects of aortic syphilis. In both instances the activity of the disease appears to fall on the further distribution of the vessel. In the first of the

2 cases the transverse portion of the arch and in the second the abdominal aorta had borne the brunt of the disease with the formation of aneurysm in both instances.

FIG. 15.—Case IX. Front view, showing prominent aortic knob only.

FIG. 16.—Case IX. Semilateral view, showing aneurysm of posterior aspect of aortic arch.

CASE IX.—Colored porter, aged thirty-four years; single; complaint: severe brassey unproductive cough, paroxysmal dyspnea, voice husky. Duration six months. Physical examination: slight tracheal tug, obscure systolic murmur at inner edge of left scapula just above its angle. Heart and chest otherwise negative. Left vocal cord paresis. Leutic infection at twenty-four. Blood Wasser-

mann strongly positive. Clinical diagnosis: aneurysm of thoracic aorta. Roentgenogram: the customary antèrior-front view of the heart (Fig. 15) revealed a decided increase in the prominence of the aortic knob but the aortic and heart shadows otherwise were normal. As this somewhat obtrusive prominence of the knob is not rare in the normal aorta, and less rare in aortic atheroma, it could not be interpreted as of diagnostic value. An anterior semi-lateral view of the aortic shadow (Fig. 16) solved the problem, revealing a well-marked aneurysmal dilatation of posterior aspect of the aorta as it curves to the left and downward. This bulging could be seen rather indistinctly with the screen, but appeared much more clear-cut on the plate. The case furnishes a good example of the importance of screening all cases and of taking plates of more than one aspect of the aorta when doubt exists.
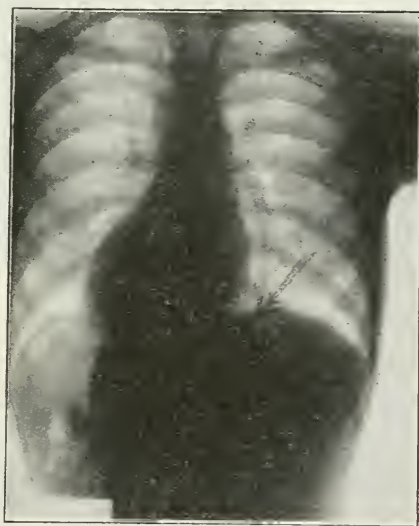
FIG. 17.—Case X. Note subcardiac shadow corresponding to abdominal aneurysm.

CASE X.—Colored porter, aged twenty-five years; complaint: pain in right hip; duration two weeks; previous health satisfactory. Physical examination revealed a plainly visible mass in epigastrium pulsating with expansile thrust synchronously with the heart's action. Luetic infection at sixteen. Blood Wassermann strongly positive.

Fluoroscopic examination, the stomach being distended with barium sulphate suspension, showed the stomach displaced to the left and pulsation of lesser curvature in contact with aneurysm.

Roentgenogram (Fig. 17) shows a practically normal heart and aortic shadow; below the heart is seen a dark shadow corresponding to the aneurysm.

The progress of the case was marked by gradual enlargement of the epigastric pulsating tumor and the formation of a large mass in the upper right abdomen, displacing the liver and right kidney downward and outward into the flank with the erosion of lower ribs posteriorly and the formation of a soft pulsating tumor in that region. Death occurred suddenly three months after admission.
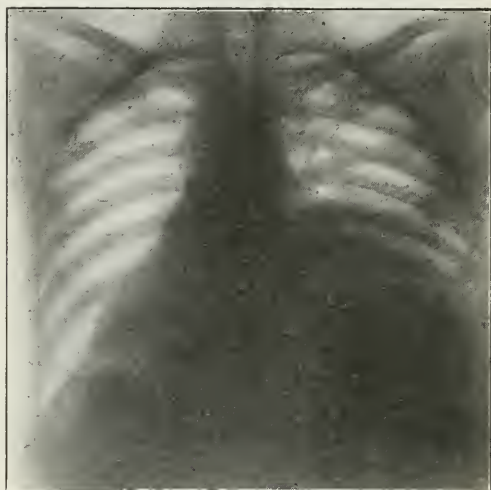
FIG. 18.—Case X.   Roentgenogram taken just before death.   Note displacement of right diaphragm with compression of right lung and displacement of heart upward. Aorta dilated.

Autopsy: Ventral saccular aneurysm of the abdominal aorta with the formation of a large false aneurysm, which contains organized blood clot weighing 990 grams. This false aneurysm is adherent to the diaphragm and right lower lobe of lung and to the eroded ribs and vertebræ. It extends down as far as the right psoas muscle. This mass is ruptured through the diaphragm near the aortic opening into the right pleural sac. A second roentgenogram (Fig. 18) was taken shortly before the patient's death. A comparison of the two roentgenograms will reveal a considerable contrast in heart contour. Upon admission the cardiac sounds were clear and heart outlines little different from normal. Toward the termination of the case the diastolic murmur of aortic insufficiency became plainly audible and the cardiac diameters increased. It is interesting to record that at autopsy no defect of the aortic valve cusps was apparent, but that the aortic ring was obviously dilated. Reference may be found in the literature to the fact that although the physical signs of aortic regurgitation exists during life, at necropsy the valves may appear surprisingly normal, regurgitation apparently depending upon dilatation of the aortic ring.

CONGENITAL ABSENCE OF LUNG.*

By A. G. Ellis, M.D.,

PHILADELPHIA.

(From the Laboratories of the Philadelphia General and Jefferson Medical College
Hospitals.)

COMPLETE absence of one lung is a rare condition. Theremin[1]
found only two cases among 30,000 autopsies in a foundling asylum
in Petrograd. Including those cases in which a tiny mass of cellular
or possibly rudimentary lung tissue capped a short bronchus, I have
found references in literature to 18 of what appear to be certain cases
of absence of one lung. In addition there are at least 5 to be classed
as possible cases, but remaining doubtful because of insufficient
description. The 18 cases are briefly as follows:

1. Haberlein:[1] Soldier, aged twenty-four years. Right lung
absent. No right bronchus. Right side of thorax filled by watery
fluid. Left lung large; both bronchi enter it. Pulmonary artery
enters undivided into left lung.

2. Haberlein:[2] Soldier, aged twenty years. Left lung absent.
No left bronchus. No left pulmonary vessels. Left side of thorax
filled by watery fluid. Right lung normal size, not diseased.

3. Hein:[3] Boy, aged six weeks, cyanotic. Right lung absent.
Rudiment of right bronchus. Right pulmonary artery and veins
absent. Defect in ventricular septum, open foramen ovale. Pul-
monary artery closed at base of heart, left lung supplied by ductus
arteriosus.

4. Stein:[4] Infant, aged six weeks. Right lung and pulmonary
vessels completely absent. Rudiment of right bronchus.

5. Bell:[5] Young man. Left lung absent. Left pleural cavity
filled by odorless fluid.

6. Maschka:[6] Child aborted at seven months; lived two hours.
Right lung absent, heart in right side of thorax. Bronchus repre-
sented by pea-sized sac. Pulmonary artery and veins entirely
absent. Left lung not lobed, otherwise normal. Esophagus ended
blind at midpoint. Atresia ani.

7. Gruber:[7] Girl, stillborn. Right lung absent. No right pri-
mary bronchus. Right pulmonary artery and veins absent. Heart
normal. Left lung no lobes, one pulmonary vein.

8. Herrero:[8] Man, aged sixty-five to seventy years. Left lung
absent. Undivided trachea continuous with right bronchus. Right
lung of enormous size.

9. Theremin:[1] Girl of eleven days. Left lung absent. Trachea
continuous with right bronchus. A small hemispherical cartilagi-

* Read before the American Association of Pathologists and Bacteriologists, May
11, 1916.

nous nodule at site of left bronchus. Right lung no lobulation. No
pulmonary veins into left auricle; they unite to form large vessel
(1 cm.) that communicates with distended vena azygos. No
deformity of chest. During life bronchial souffle and subcrepitant
rales heard over both sides thorax posteriorly.

10. Theremin:[1] Girl, aged one hundred and twenty-seven days.
Left lung absent. Trachea continuous with right bronchus. Carti-
laginous elevation size of a pea at site of left bronchus. Left pul-
monary artery and veins absent. Right lung imperfectly separated
into two unequal lobes. Left auricle no veins, vein from right lung
emptied into vena azygos. During life vesicular breathing heard on
left side.

11. Gruber:[9] Female fetus; premature birth; did not breathe.
Left lung absent. Trachea divided into three branches in hilum of
right lung. Right lung not lobed. Pulmonary artery divided into
right branch and ductus arteriosus. Heart normal, except only one
vein into left auricle (came from lung in two branches).

12. Miller:[10] Male, aged four weeks. Left lung size of a pea,
hanging on a thin bronchus. Pneumonia of right lung.

13. Miller:[10] Male, aged six weeks. Left lung size of cherry,
hanging on a narrow bronchus.

14. Miller:[10] Female, aged two days. Left lung a mass of tissue
2 cm. in diameter, attached to narrow bronchus.

15. Tichomiroff:[11] Woman, aged twenty-four years. Died of
pneumonia. Left lung absent. No primary bronchus. Trachea
divided into three bronchi just before entering right lung. Heart
normal.

16. Hanson:[12] Female child, full term, lived fifteen minutes. Left
lung absent. Bronchus one-twelfth inch long, mass on end size of
buckshot. Right lung rather smaller than usual. Heart on right
side. Diaphragm lacking on left side with lower portion of small
intestine and part of colon in left pleural cavity; appendix just
beneath clavicle.

17. Findlayson:[13] Child lived some hours after birth. Right lung
absent. Trachea ended in left bronchus. Pulmonary artery and
veins undeveloped. Left lung hypertrophied, pushing heart to
right.

18. Gross:[14] Boy, aged five months, twenty-three days. Left
lung absent. Left bronchus 1 cm. long; blind; end rounded. Left
pulmonary artery and veins absent. Heart normal. Right lung
filled right thorax, mediastinum, and small part of left thorax; no
definite lobulation. Thorax symmetrical. Other lesions included
left-sided hypoplasia of face, dermoid of left eye, anomalous right
renal artery, and atresia ani.

Doubtful cases of absence of one lung are those of Sömmering,
Riviere, Pozzi, Heyfelder, and Meckel, quoted by Fürst. Some
writers accept these, some do not.

Through the courtesy of Dr. W. C. Hollopeter, I am enabled to add the following case, which occurred in his service at the Philadelphia General Hospital. The clinical notes are abstracted from those of the interne, Dr. Marek.

19. F. M., boy, aged eight years. Admitted November 7, 1915. Good proportion and development, but poorly nourished. Family and previous history negative. Sick one week prior to admission, with chills and fever. Complains of pain in left knee and muscles of legs. Left knee slightly swollen.

Chest expansion fair, but diminished on left side. Lungs: except at apex, dulness posteriorly on left side extending to midaxillary line; no dulness at apex in front or posteriorly; tubular breath sounds heard posteriorly as far as midline of left side. Right lung: no dulness; breath sounds harsher. Heart: apex displaced to midaxillary line and in fourth interspace. Right border two inches to left of sternum. Accentuated second sound. Blowing systolic murmur, heard best at apex and transmitted to left. Heart sounds heard well over area of dulness described in back. Diagnosis: Acute articular rheumatism; acute endocarditis.

November 8. Dulness in back over left lung is marked and no breath sounds audible at base. Above root of lung tubular breathing. Right lung normal except for exaggerated breath sounds. Cardiac impulse over thoracic wall in midaxillary line. Roentgen-ray examination: There is effusion of the left side of the chest. The heart cannot be defined owing to shadow of fluid.

November 9. Two attempts to aspirate fluid from pleural cavity failed.

November 12. Breath sounds audible when puncture was made, but not in midaxillary line when murmur was loud and pronounced.

November 13. Retraction of intercostal muscle in fourth interspace of left side.

November 14. Breath sounds more audible over apex of left lung.

November 19. Death.

The body came to autopsy November 20, with the following clinical diagnosis: Acute articular rheumatism; acute endocarditis; pericarditis with effusion; pleurisy with effusion.

The autopsy notes bearing on the condition here reported are briefly these:

Diaphragm is at fifth interspace on each side. Removal of sternum reveals pulmonary tissue occupying entirely the exposed area. The right pleura anteriorly and laterally has firm adhesions. The left lung is absent, the right lung extending well beyond the left costochondral line and the large pericardial sac occupying the remainder of the left side of the thorax. The pericardium contains 75 c.c. of serum. Left branch of pulmonary artery and left pulmonary veins are lacking. Two veins from right lung enter left auricle.

The right lung (Fig. 1) is large, the upper lobe being approximately twice the usual size. A projection to the left from the upper extremity forms a second apex half the width of the right, the former extending beneath the left clavicle and first rib. At the lower margin of the upper lobe is a projecting tongue, 3 by 3 cm., forming a rudimentary lobe. The middle lobe is of the usual size, but projecting partly from it and partly from the upper lobe is a lobe-like mass 3 by 4 cm. Roughly speaking the lung has a sem-

Fig. 1.—Malformed right lung, left lung absent. Postero-internal view. The lung especially the upper lobe, is large. There are two apices, the left longer and more pointed; this extended under the left clavicle and gave left apical breath sounds. Left bronchus 2 cm. long, terminating in a small mass of rudimentary lung tissue.

blance of five lobes. The lower lobe is large and has a number of small subpleural hemorrhages. The diaphragmatic surface of the lower lobe has a thin covering of fibrin. There is no evidence of consolidation. The right primary bronchus is normal. The left, which is a trifle smaller, ends 2.5 cm. below the bifurcation in a blind pouch of soft, grayish tissue, 1.2 by 0.7 cm. in size.

The heart, other than huge vegetations on the mitral leaflets, shows no noteworthy abnormality.

Anatomical Diagnosis: Acute vegetative mitral valvulitis; hydro-
pericardium; chronic adhesive pleuritis of right side, with acute
fibrinous pleuritis at base; absence of left lung; hypertrophy of right
lung; cloudy swelling of heart and kidneys; fatty infiltration,cloudy
swelling, and red infarct of liver; multiple embolic infarcts of kidneys
and spleen; embolic gangrene of three small toes of left foot.

Sections through the terminal portion of left bronchus and the
tissue over it show a bronchial wall containing cartilage surmounted
by cellular connective tissue without muscle or glands.   The surface
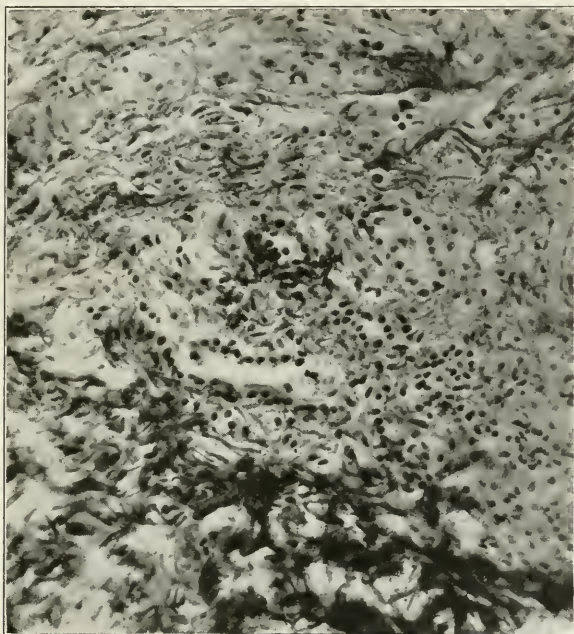
FIG. 2.—Section of tissue covering end of short left bronchus.   Near center are
several indistinct spaces lined by cuboidal epithelium that probably are rudimentary
alveoli.

is partly covered by cuboidal or low columnar epithelium.   Sur-
mounting the bronchus is soft, cellular fibrous tissue, with occa-
sionally an illy defined space (Fig. 2) lined by epithelium, suggestive
of alveolus or bronchus, but not typical of either; rudimentary lung
tissue appears the best term to apply to it.

Of these 19 cases of absence of one lung, 13 were of the left and
6 of the right, showing a predilection for left-sided pulmonary
aplasia that is not satisfactorily explained on anatomical grounds.
Interference with blood supply in early embryonic life is supposed to
be the cause in all cases.

Anomalies other than those of the bloodvessels directly concerned were present in some of the cases, but not in others. In all of them the chest externally was symmetrical, the opposite lung, the heart, or fluid taking the place of the missing organ; in one, part of the intestines were in the thorax. This is important as increasing the difficulty of diagnosis during life and is also an argument against the case of Chilaiditi[15] being one of pulmonary aplasia. His patient is a boy, aged ten years, in whom he has diagnosticated agenesis of left lung by the roentgen rays. The left half of the thorax is flattened, however, and the left shoulder is lower than the right. Chilaiditi[15] admits that in such a case one would naturally think first of inflammatory contraction as the cause of the deformity, but says the physical signs in his patient are against this supposition. There is no difficulty in breathing, and percussion gives a clear note anteriorly two fingers beyond the middle line to the left. Posteriorly there is paravertebral clearness 2 to 3 cm. on the left side, otherwise there is absolute dulness. There is bronchial breathing over the left apex. The heart boundary is not to be determined by percussion. The apex beat is probably at the level of the nipple and 2 cm. toward the axillary line.

Meyer[16] believes he has under observation a case of aplasia of the left lung in a man, aged twenty-seven years. The subject has a well-developed thorax. The apex beat is in the midaxillary line. There is normal lung resonance anteriorly except in the left supraclavicular region (where there is slight dulness) and over the heart. Posteriorly there is complete dulness on the left side except a zone two and a half fingers broad along the vertebral column from the sixth to the twelfth rib. Meyer believes the diagnosis of aplasia of the left lung is substantiated by the roentgen-ray findings. He states that if the condition is acquired the thorax usually sinks in while in congenital cases, or real aplasia, the other lung hypertrophies and prevents sinking, hence the chest is symmetrical. Neisser has observed in the Stettin Hospital a case essentially like that of Meyer.

It may be, therefore, that the diagnosis of absence of a lung may be made clinically, although this has not yet been done and proved by autopsy. The usual enlargement of the one lung furnishes the presence of pulmonary tissue and its physical signs on the side of the absent organ; this does not suggest to the clinician the lack of an entire lung. The extreme rarity of the condition, of course, renders it unobtrusive as a possibility.

The duration of life in cases of absence of one lung is usually short, but this probably depends partly upon other circumstances. The condition is not incompatible with adult life, one of the subjects being twenty years, two each twenty-four years, and one sixty-five years of age; another is recorded as being a "young man."

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THE USE OF IMMUNE SERUM IN THE TREATMENT OF WHOOPING COUGH.*

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VERY satisfactory results with immune serum have been obtained in two diseases of lower animals: in epidemic jaundice the blood of guinea-pigs which have recovered from this disease will inactivate the virus, active blood being neutralized by one-hundredth part of convalescent's blood.[1][2] In hog cholera immunity is conveyed by injections of convalescent's blood,[3] which becomes life-long upon the addition of antigen such as the blood or tissues of an active case.[4]

In no disease in man have such results been obtained with immune blood. In scarlet fever, when used early in cases that have not become septic in type, results have occasionally been obtained; these are not yet consistent.[5][6][7][8][9][10][11][12][13][14][15][16][17][18] Mixed convalescent's blood has been used in measles.[19] Protective powers have been observed in mumps from small doses (6 to 8 c.c.) injected into muscle[20] in an institutional epidemic in which 33 per cent. of (134) susceptible children contracted mumps; no case occurred among those (17 children) treated. The blood of animals (cat) inoculated with saliva from cases of human parotitis is found to modify the course of such inoculations in other animals.[21] In

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* Read at the second annual meeting of the Central States Pediatric Society, in St. Louis, October 18, 1916.

poliomyelitis convalescent's blood will inactivate the virus;[22] immune substances have been found both in the blood of monkeys[23 24 25 26] and human beings,[27] and therapeutic properties were seen when the administration of the serum was made within eighteen to twenty-four hours after the inoculation of the virus into the brain or nose.[28] In a recent summary of this work in poliomyelitis[29] it is said that in the case of monkeys in which the virus does not exceed a certain dose the disease can be prevented or the onset of paralysis delayed. Human serum is found effective for monkeys.[30] A series of 32 human cases in which immune serum from human cases was injected intraspinally is reported;[31 32 33] there occurred in these about the same incidence of deaths, paralysis, and recoveries as occur among cases not so treated; there is another series of 4 cases with similar results,[34] and a report of 2 cases in which serum was used from persons who had recovered years before[35] (it is said that the neutralization test remains positive after poliomyelitis for a number of years*).[36] Convalescent's blood has been used in epidemic meningitis[37] and in pneumonia[33] without great success.

Because of these data it seemed worth while to try this method of treatment in whooping cough. It is now usually thought that whooping cough is a specific infectious disease; during the course of the second or third week, antibodies appear which are specific by agglutination[39] and by complement tests.[40 41] For the purpose of determining the value of this method, injections of human blood were carried out in the early weeks of this disease in 45 cases. These were divided into three groups of 15 cases each. In Group A the blood injected was from persons who were convalescent or who had recovered from whooping cough within three months. In Group B the blood was from persons who had had the disease at more remote periods, and in Group C from persons who, so far as they knew, had never had it. Groups B and C were designed as controls to A.

The ages of the children in all groups averaged under three years: in Group A, in which convalescent's blood was used, 5 were in the first half year of life, 1 was five weeks old, and 1 thirty days old. The stage of the disease at which the treatment was given was about the same in the three groups; in Group A it was begun in the first week in 2 cases, in the second week in 5 cases, in the third weeks in 7 cases, and in the fourth week in 1 case. Dosage was gauged in a rough way to body weight of donee, from one-tenth to one-fifth of the computed volume of blood of donee was given; this varied between 40 and 125 c.c., divided into two, three, or four doses and injected into muscle (gluteus). Discoloration often followed the injections in very young infants; in a few there was

* Since this bibliography was prepared, another series of 15 cases has been reported (C. W. Wells: Jour. Am. Med. Assn., October 21, 1916, No. 17, lxvii, 1211).

induration for a day or two; there were no infections, and temperature reactions insofar as could be told in this disease did not occur. The injections in every case were completed within a week in order to avoid hemolytic reactions; reactions to new proteins were not observed. The blood used was from a single donor in ten, from two in four, and from three in one. Blood not used at once was citrated to 1 per cent. (in this amount sodium citrate is said not to affect antibody).[42] The usual examination of donors, including Wassermann reactions on the bloods of non-relatives, were made.

The results of the treatment in the three groups may be summarized: In Group A of 15 children whose average age was twenty-eight months, who received convalescent's blood during the early weeks of whooping cough, there occurred no deaths and no serious complications; the course of the disease was, however, in no definite way different than is usually seen, and was not appreciably influenced by the treatment except in 3. This is a very small proportion, and it is more than likely that in 15 cases 3 of them might very well run an unexpectedly mild course without attracting a great deal of notice. The blood pictures of 2 of these, however, was interesting: In Case 4, during the third week of the disease, a 50,000 white count came down after 60 c.c. of convalescent's blood to 18,000 and the mononuclear percentage fell from 74 to 50; this drop was coincident with clinical improvement; this was a hand-fed baby of five months who weighed but 3860 grams.

In Cases 8 and 11 a transitory hyperleukocytosis followed injections of the blood, and was succeeded in each instance by a drop to well below the original counts; changes in mononuclear percentages accompanied these drops. The shortest course of any of these cases was that of Case 11, four weeks; no shortening of the course of the disease was seen in any of the others.

In Group B, in Case 1, in which the blood used was from the mother who had had pertussis twenty years before, quite as satisfactory improvement occurred as in any case in Group A; in this group there were two pneumonias which recovered. There were also two pneumonias in Group C with one death, and in this group there was one case which seemed to have been very favorably affected by the injections of normal blood.

In explanation of these results it may be said that in some diseases injections of normal blood have brought about improvement, and that immunity may be increased at times by injections of normal blood,[43] that this has also occurred after injections of other things, such as protease,[44] lipase, ferments (trypsin), or drugs (kaolin).[45][46] Hyperleukocytosis, such as occurred in several cases in this series, has assisted immunity in other diseases (arthritis, typhoid[47][48]), so for lack of consistency in the results obtained in these cases of whooping cough it is not possible to ascribe any of them to a specific action of the blood injected.

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AURICULAR FIBRILLATION: SOME CLINICAL CONSIDERATIONS.

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Auricular fibrillation is a condition in which numerous irregular, very rapid impulses are sent out by the auricles. The auricles do not actually contract, but, on the contrary, remain twitching in diastole. The ventricles, however, respond to a small portion of the impulses and contract in a grossly irregular fashion both as to rate and strength. The condition has been called "delirium cordis" and "pulsus irregularis perpetuus." In the great majority of cases it is easily recognized by auscultation at the apex and palpation of the radial pulse. The absolute arrhythmia heard over the precordium, generally with a rate over 100 (when the patient is first seen), together with a pulse deficit (difference between the apex and radial counts) in a patient with cardiac failure indicate that the auricles are fibrillating. In not more than 10 per cent. of the cases, according to Lewis,[1] will the above proposition not be true and in not more than 10 per cent. will this condition be confused with other arrhythmias, especially numerous extrasystoles. Considerations that will appear later in this paper will help to diminish this error still further.

During the past several years considerable work has been done, using the newer methods of cardiac diagnosis, which has given us a clearer conception of auricular fibrillation. The great importance of this condition is indicated by its frequency, 128 different cases having been observed at the Peter Bent Brigham Hospital in thirty months; while during the same period of time there were admitted 146 cases of such a common disease as lobar pneumonia. These figures become more striking when one considers that the cases of pneumonia are not apt to return, while the cardiac cases keep coming back frequently to the wards, though in the figures given above readmissions are not included. In fact, it is not a rare occurrence to see 10 cases of auricular fibrillation at one time in the wards where there are about eighty beds. Its importance is also indicated by the fact that it is generally a permanent irregularity, and if untreated, seriously embarrasses the circulation. At the same time it can be said there is no group of cardiac cases that responds so well to proper treatment.

For the above reasons a clinical study has been made of all the cases of auricular fibrillation observed at the Peter Bent Brigham Hospital during a period of two and a half years. Only those

[1] From a lecture given at the Peter Bent Brigham Hospital, October, 1914.

cases have been considered in which the diagnosis was made by electrocardiographic tracings. The special points that were sought for in analyzing the records were a previous history of rheumatic fever or chorea, the presence of organic mitral disease, and the age of the patient. It became a matter of interest whether any data of diagnostic or prognostic value could be drawn from a large group of cases by studying the relation between the presence or absence of a past history of rheumatic fever, the signs or lack of signs of organic mitral disease, and the age of the patient. Other clinical points, such as the importance of syphilis in auricular fibrillation and the differentiation between organic and relative mitral insufficiency, also have been considered.

As will be shown below, there seemed to be a fairly intimate relationship between the previous history of rheumatic fever and the subsequent development of organic mitral endocarditis (generally mitral stenosis), with the inception of auricular fibrillation. Lea[2] several years ago, using polygraphic tracings in his study of 69 cases of auricular fibrillation, found rheumatic fever or chorea in 56.6. per cent. There was another definite group of cases in our series in which there was no history of rheumatic fever, no signs of mitral disease, and auricular fibrillation was present; these were all cases of cardiac sclerosis or chronic myocarditis. In the entire series there were 128 cases equally divided between males and females, i. e., 64 males and 64 females. (See Table.) The average age of all the cases was 47.3 years (ranging from seventeen to seventy-five years). The average age of the males and females was practically the same, 48 for the former and 46.6. for the latter.

Syphilis as an Etiological Factor. The role that syphilis plays as an etiological factor in auricular fibrillation was found not to be very important. There were only 11 cases that had a positive Wassermann reaction, i. e., 8.6 per cent., the test having been done as a routine on all cases. When we compare this figure with the general average of all cases admitted to the medical wards, which according to Walker and Haller[3] was 12 per cent., we see that syphilis was less common in cases of auricular fibrillation than in those not having it. The 11 cases consisted of 2 with aneurysms of the aorta, 2 of syphilitic aortitis, and 7 which either had chronic myocarditis or chronic mitral endocarditis, or both. It is noteworthy that a fair number of chronic heart cases when first seen have an enlarged liver resulting from a relative regurgitation through the tricuspid valve and become jaundiced. A positive Wassermann reaction under these circumstances may later prove to be negative if repetition is made after the jaundice has disap-

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[2] Some Points in Relation to the Etiology of Auricular Fibrillation, Quart. Jour. Med., 1910-11, iv, 423.

[3] Routine Wassermann Examination of Four Thousand Hospital Patients, Jour. Am. Med. Assn., 1916, lxvi, 488.

peared. This happened in at least one of our cases. It is evident from these figures that syphilis plays an unimportant part in the etiology of auricular fibrillation.

Statistical data.	Number of cases.	Per cent.
Auricular fibrillation	128	
Persistent auricular fibrillation	110	85.9
Transient auricular fibrillation	18	14.1
Males	64	50.0
Females	64	50.0
Average age of males (limits seventeen to seventy-five years) . .	48.0	
Average age of females (limits twenty to seventy-two years) . .	46.6	
Wassermann positive in the blood	11	8.6
Persistent Auricular Fibrillation:		
Group I. Rheumatic history and mitral endocarditis	39	35.5
Males	15	
Females	24	
Average age of males	35.0	
Average age of females	38.4	
II. No rheumatic history and no mitral endocarditis . .	34	30.9
Males	23	
Females	11	
Average age of males	57.5	
Average age of females	58.9	
III. Unclassified	37	33.6
Total number of cases in Groups I and III with definite rheumatic history	48	43.6
Autopsy Examinations:		
Hearts examined	261	
Over fifty years of age	107	
Showing chronic mitral endocarditis	2	
Under fifty years of age	154	
Showing chronic mitral endocarditis	21	

TRANSIENT AURICULAR FIBRILLATION. Although auricular fibrillation was at first considered a permanent irregularity, and was called "pulsus irregularis perpetuus," it is now quite definitely known that it need not be so. In fact, K. Fahrenkamp,[4] in a review of 120 cases of auricular fibrillation, all diagnosed by electrocardiograms, found 4 transient cases i. e., 3.5 per cent. It is necessary at this point to decide what is to be called transient and what permanent auricular fibrillation. There are some cases which have definite repeated attacks of palpitation and tachycardia just like the ordinary paroxysmal auricular tachycardia, except that the heart's action is absolutely irregular. Short periods of fibrillation are often observed in cases of auricular flutter after digitalis has been given and before the normal rhythm is resumed. Transient auricular fibrillation also occurs under very varied conditions, i. e., during acute rheumatic fever, postoperative, in hyperthyroidism, etc. In addition it is observed rarely as a terminal event lasting from a few hours to a few days. All cases of this series that have not been observed to become regular in rhythm have

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[4] Vorübergehende komplette Herzunregelmassigkeiten unter dem klinischen Bilde der Arhythmia perpetua mit Boebachtungen über Vaguswiskung, Deutsch. Arch. f. klin. Med., 1914, cxvii, 1.

been considered as cases of permanent auricular fibrillation, and those that were definitely proved to have returned to a normal rhythm were grouped as transient. Of the 128 cases, 110 were persistent and 18 were transient (14.1 per cent.). This is a much higher figure than has heretofore been noted.

One has to exercise the greatest care in making the diagnosis of transient fibrillation. If one depended on polygraphic tracings or merely on auscultation frequent errors would be made, as has been shown by Fahrenkamp.[5] Numerous extrasystoles together with a sinus arrhythmia might cause a very irregular pulse, and this would change into a normal rhythm, with rest in bed and simple sedatives, as the extrasystoles disappeared. This, of course, wrongly would have been considered a case of transient fibrillation. Then, again, if an absolutely irregular heart action becomes perfectly regular, as determined by auscultation or palpation of the radial pulse, it is no proof that the auricles have stopped fibrillating. Two cases of this series acted in such a way, and at first were thought to be transient cases. This was supposed to have been brought about by digitalis. Careful examination of the electrocardiograms showed that the auricles were still fibrillating, but that there was complete auriculoventricular heart-block with a regular ventricular rhythm. In both of these cases the ventricular rate was rapid, which did not make one immediately think of an idioventricular rhythm. The possibility of a rapid regular ventricular rate in auricular fibrillation is mentioned by Lewis.[6] The ventricular rate of the first case was 62 and that of the other was 110. Furthermore, the frequency with which transient fibrillation will be noted will in a great measure depend on how carefully the heart rhythm is observed and how frequently electrocardiograms are taken. This might explain the comparatively high incidence of transient cases found in this series.

Of the 18 cases of transient auricular fibrillation here observed, 1 occurred during the lysis of pneumonia, similar to one of the cases described by Krumbhaar,[7] 1 in hyperthyroidism, 1 postoperative (avulsion of the sensory root of the trigeminus for trigeminal neuralgia),[8] 2 during acute rheumatic fever, 4 following auricular flutter, 4 as a result of active digitalis therapy, and 6 were spontaneous or idiopathic cases. Among these latter there were 3 who had chronic myocarditis (2 with and 1 without chronic nephritis similar in type to the cases described by Robinson);[9] 1 had cancer of the esophagus, 1 chronic alcoholism, and 1 chronic

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[5] Loc. cit.

[6] Clinical Electrocardiography, London, 1913, p. 95.

[7] Transient Auricular Fibrillation, an Electrocardiographic Study, Arch. Int. Med., 1916, xviii, 263.

[8] This last case is counted twice because the fibrillation followed a short period of auricular flutter.

[9] Paroxysmal Auricular Fibrillation, Arch. Int. Med., 1914, xiii, 298.

endocarditis of the aortic and mitral valves. Cohn[10] has observed transient fibrillation during pneumonia in a large portion of his cases, 12 out of 123, 7 of whom had had no digitalis. Two interesting cases have been observed during the past year who were not patients in the hospital and have therefore not been included in this study. They complained of frequent attacks of palpitation, otherwise they were well. Nothing abnormal could be found on careful examination except the arrhythmia, which was a transient auricular fibrillation. Both happened to be well developed athletic young men. Gossage and Hicks[11] refer to the possibility that patients previously well may suddenly develop auricular fibrillation. It therefore can be stated that the transient form of auricular fibrillation may exist in otherwise normal individuals as well as under many various abnormal conditions.

On careful questioning one is impressed by the frequency with which patients suffering from auricular fibrillation have complained of previous attacks of palpitation. Quite often the symptoms of shortness of breath, pain in the chest, cough, etc., have had a sudden onset, and they were not always precipitated by exertion. In fact, some of the patients complained that the trouble was first noticed when they suddenly awoke during the night and found the heart palpitating. In some cases the history of attacks of palpitation was repeated, with periods free from symptoms in between, and extending over one or more years before the permanent state was assumed. In others there was no repetition of the attacks, and on the contrary the symptoms of circulatory failure seemed to date definitely from the onset of auricular fibrillation. It would seem that many of the cases of permanent fibrillation have gone through transient attacks and that the symptoms complained of by the patient are intimately connected with the occurrence of the irregularity.

PERSISTENT AURICULAR FIBRILLATION. There were 110 cases of persistent fibrillation which arbitrarily have been divided into three groups. The first includes all cases who had a definite history of rheumatic fever or chorea and had signs of chronic organic mitral disease. The second includes all those who gave no history of rheumatic fever or chorea and who were diagnosed[12] as having no organic mitral disease. The third group includes all of the remaining cases. One is immediately impressed by the natural obstacles to such a classification. The histories are taken by different house officers. Occasionally one forgets either to ask or at least to record definitely whether the patient had or had not

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[10] Irregularities in Pneumonia. Unpublished.

[11] On Auricular Fibrillation, Quart. Jour. Med., 1912–13, vi, 435.

[12] In all these considerations the diagnosis taken was the one which was finally made by Dr. H. A. Christian, physician-in-chief, who saw the larger part of the patients, examined the records, and approved of the diagnoses of all the cases.

had acute rheumatic fever or chorea, although it must be said that
in all but a few cases there was some statement on this point.
Furthermore, some patients knew very little English and probably
answered to questions they hardly understood. Finally, one might
obtain a history of rheumatic pains or rheumatism. This was
generally followed by a short description of the condition which
identified it; but unfortunately this description was lacking in
some instances and was unsatisfactory in others, so it was decided,
in this study, to include in the first two groups only those cases in
which a definite statement was made and which had the two quali-
fications required as mentioned above. If a case had a definite
history of rheumatic fever and had no evidence of mitral disease
it fell in the third or exceptional group; if the past history was
vague, or the clinical diagnosis doubtful, it was included in this
last group.

It was found by this method that 39 cases (15 males and 24
females), or 35.5. per cent., of the cases of permanent fibrillation,
fell in the first group, i. e., having a definite history of one or more
attacks of rheumatic fever or chorea and showing signs of chronic
mitral endocarditis. Most of these showed definite evidence of
mitral stenosis, generally with mitral insufficiency. Two cases
were included here with some hesitation, because although there
was definite evidence of organic aortic disease the signs over-
shadowed those of mitral disease. They both had loud murmurs
of aortic stenosis and aortic insufficiency which were best heard
at the base but were also present at the apex of the heart. The
question as to whether there was organic mitral endocarditis was
in doubt. The Wassermann blood tests were negative; one of the
patients had had four attacks of rheumatic fever and the other
one attack. In this respect they stand out as the only rheumatic
patients who had auricular fibrillation in whom the question as to
whether the mitral valve was involved was uncertain, when there
were definite signs of valvular disease. These 2 cases were in-
cluded in Group I, with the positive cases of mitral disease because
the endocarditis was undoubtedly rheumatic in nature. The
average age of the females in this group was 38.4, that of the males
35; the former were decidedly more numerous. There were only
2 cases over fifty years of age. One was a man, aged fifty-five
years, who had three attacks of rheumatic fever at the ages of
sixteen, forty-three, and fifty-two. He had been doing very hard
physical work all his life up to the age of fifty-two years. It might
well be that the first attack of rheumatic fever did not affect his
heart, which would account for the late occurrence of the auricular
fibrillation and the mitral disease. The other was a woman, aged
fifty-six years, who belonged to a higher class in society than the
average hospital patient. She had had rheumatic fever at the
ages of four and thirty and chorea at twelve years. During which

infection her heart became involved it was impossible to tell. In this connection it is of interest to note that Kemp,[13] following his cases over a considerable period of time, found that 23 per cent. of them went through one or more attacks of acute articular rheumatism without clinical affection of the heart. Therefore it can be said that about one-third of the patients with permanent auricular fibrillation had both a rheumatic history and organic mitral disease, and all but 2 of this group were comparatively young.

Thirty-four, or 31.2 per cent. of the cases, were placed in the second group, i. e., having no history of rheumatic fever or chorea and having no signs of chronic organic mitral disease. They were practically all cases of chronic myocarditis with or without chronic nephritis and hypertension. They frequently showed signs of peripheral arteriosclerosis. Of these there were 23 males and 11 females. The proportion of males to females is just opposite in the two groups, there being a marked preponderance of females in the first and of males in the second group. The average age of the males of the latter group is 57.5 and that of the females 58.9. This is about twenty years more than the average age of the first group. The youngest was forty-four years and the oldest seventy-five. The number of cases that could thus be put into one or the other of these two groups was 73, or 66.4 per cent. of all patients with persistent auricular fibrillation. It seems quite striking that with such narrowly limited criteria as a basis of division so large a percentage of cases could be definitely grouped. It is observed that special emphasis has been put on the fact that the valve lesion must be *chronic* and *organic*. The reason for this is that not infrequently one finds fresh minute vegetations on the mitral or aortic valves, which otherwise appear normal, and which indicate a terminal endocarditis. This, of course, could not have any important influence in the causation of the auricular fibrillation. Again, a very important consideration is the difference between organic and relative mitral insufficiency. A loud, blowing systolic murmur is frequently heard at the apex, which is transmitted to the axilla and often well heard all over the precordium. This is a common finding in senile hearts or cases of chronic myocarditis, especially if there is an associated hypertension. It signifies a functional insufficiency of the mitral valve due to a temporary or permanent dilatation of the mitral ring, but it is often confused with an organic mitral regurgitation. There does not seem to be any very definite method of differentiating the one from the other, and so one has to weigh whatever evidence there is at hand. It is for this reason that the above considerations and the autopsy findings discussed below are of some importance. If a patient is sixty years old and has no history of rheumatic fever, it is very unlikely that he has

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[13] On the Prognosis of Acute Articular Rheumatism, with Special Reference to the Cardiac Manifestations, Quart. Jour. Med., 1913–14, vii, 251.

any organic mitral disease, even if there may be heard a very loud systolic murmur all over the precordium. On the other hand if the patient is thirty years old and has a definite past history of rheumatic fever or chorea and auricular fibrillation is present a systolic murmur at the apex would indicate that there was an organic mitral endocarditis. In fact, a few of the senile cases of this series were considered by some observers to have organic mitral regurgitation because of loud systolic murmurs, and showed normal valves in postmortem examination. The distinction between relative and organic mitral insufficiency is not of much importance in senile hearts, but is of considerable prognostic significance in the cases of the first group. In this group we found only two patients who were over fifty years of age, and practically all were suffering from cardiac insufficiency. Only 6 of the 39 failed to develop signs of mitral stenosis. A diagnosis of organic mitral regurgitation in a middle-aged or young person signifies that mitral stenosis may very likely develop and that the prognosis as to length of life is generally discouraging.

The third group is the most interesting because it contains the doubtful cases, and it is here that some of the above considerations can be of help in the diagnosis. Several of them readily fall into one or the other of the first two groups if studied carefully and when some questionable points are definitely determined. There were 37 cases that did not correspond to either of the first two groups. No satisfactory history was recorded, or there was a diagnosis of organic mitral disease in the absence of a history of rheumatic fever, or there was no organic mitral disease in the presence of a definite history of rheumatic fever. A careful study of these cases trying to apply the two general principles is very enlightening, *i. e.*, that a young patient who has auricular fibrillation and a definite rheumatic history very likely has chronic organic mitral disease; and secondly, that an elderly patient who has auricular fibrillation without a past history of rheumatic fever very probably has no organic mitral disease (although frequently there is a relative functional mitral insufficiency). One might further add that if a patient over fifty years old had definite signs of mitral stenosis and auricular fibrillation, very likely there was a previous history of rheumatic fever or chorea, and that this infection involved the heart late in life.

Of the 37 unclassified cases, in 6 no mention was made as to whether the patient did or did not have rheumatic fever. No further statement need be made concerning them except that there were none over fifty years of age with organic mitral disease. There were 9 who had a definite history of rheumatic fever or chorea, and yet were diagnosed as having chronic myocarditis without organic mitral disease; some of these were definitely diagnosed relative mitral insufficiency. A consideration of the

ages of these patients is very significant. One would expect that if these patients did not develop organic mitral endocarditis as a complication of the rheumatic fever (reference has been made above to the observation of Kemp[14] that 23 per cent. of rheumatics do not develop heart disease) they would belong to the group of senile hearts and average over fifty years of age. This was true of all cases except one. This was a woman, aged thirty-two years, who had chorea at the age of ten and rheumatic fever at twenty-four years. She had been complaining of dyspnea on exertion and occasional swelling of the legs, which conditions were gradually becoming worse. On physical examination a blowing systolic and a distinct diastolic murmur were heard by three observers on three different occasions. At no time was it noted that the murmurs were absent. The first heart sound at the apex and the second sound at the pulmonic area were not accentuated. Here it seems that there was sufficient evidence for a diagnosis of organic mitral endocarditis which would bring the case into Group I. Two other cases of this series were of particular interest because the house physician recorded a past history of acute rheumatic fever in them. They were both seen by the author, and one was particularly questioned on this point. His history was that of frequent attacks of acute pain in his big toes, with tenderness, redness, occasionally fever, and sometimes with involvement of the fingers. He was a typical case of gout having a very high uric acid content in his blood. The history of "acute rheumatic fever" was more likely that of acute gout. An autopsy was subsequently performed on this case and the mitral valve was found to be essentially normal. The heart was considerably hypertrophied and showed chronic cardiosclerosis. The other case with a rheumatic history was also one of gout having arteriosclerosis and chronic myocarditis without organic mitral disease. Here again the past history of frequent attacks of acute rheumatic fever might well have been that of acute gout. These 2 cases quite certainly belong to Group II. The remaining 6 of the 9 patients, who had auricular fibrillation, chronic myocarditis without organic mitral disease, and a definite history of rheumatic fever, exemplify the type in whom rheumatic fever did not injure the mitral valve, and its effect on the myocardium is questionable. If it is assumed that these 6 patients completely recovered from the rheumatic fever without injury to the heart, as is very probable, they can be considered as cases of auricular fibrillation coming as a result of chronic myocarditis with arteriosclerosis.

Five patients of this unclassified group had vague past histories; several had mild rheumatic pains or rheumatism, one had growing pains, and one did not know which diseases he had had.

[14] Loc. cit.

Although nothing definite can be said about them, it happens that the only one over fifty years of age had chronic myocarditis without any valve lesions, while the other four had organic valvular disease. Here again the difference in age incidence in the two types of auricular fibrillation is well shown, the younger ones having valvular disease and the older myocarditis.

There still remained 17 of the exceptional cases which have all been diagnosed chronic mitral endocarditis. These definitely had neither rheumatic fever nor chorea. Three had frequent attacks of acute tonsillitis. In the remaining 14 there was no previous history of any of the acute infections which are regarded as the common causes of endocarditis. No importance was attached to a history of mild sore throats which a large majority of all hospital patients evidently have had. A study of these 17 cases brought out some points worthy of mention. There were 6 over fifty years of age among them. Two were definite cases of mitral stenosis. A third which was diagnosed mitral stenosis returned eighteen months later and showed no evidence of mitral disease. A fourth, which was discharged as mitral insufficiency and questionable mitral stenosis, was examined one year later and only a blowing systolic murmur was heard. A fifth was a woman, aged sixty-seven years, who was thought to have chronic myocarditis, chronic nephritis, hypertension, and mitral stenosis, although at no time did she show a diastolic murmur or thrill. The first sound was sharp and suggested mitral stenosis. Her local physician, who had seen her at home, wrote that he had not found evidence of mitral stenosis. There certainly is some question as to whether she had endocarditis. The sixth was considered a case of chronic myocarditis with mitral insufficiency. No definite statement was made as to whether the insufficiency was relative or organic in nature. As was stated above, there generally is no way of deciding this latter point on physical signs, but as a result of the study of 261 autopsies, which will be discussed below, the age and absence of any rheumatic history point strongly against organic valvular disease. Of the 11 remaining cases who had no history of rheumatic fever under fifty years of age, 10 had definite evidence of mitral stenosis with or without accompanying aortic disease, and they all had mitral insufficiency. It can therefore be said that of all the cases of permanent auricular fibrillation there were only 4 over the age of fifty years who had definite organic mitral disease.

TREATMENT. It is well understood by all clinicians that in the treatment of heart disease one should not interest himself in treating an irregularity. The most important aim is to help the heart muscle. In this connection auricular fibrillation plays a very important role, for the irregularity results essentially in a rapid ventricular rate if the condition is left untreated. This rapid rate tires out the heart, and although the patient at first may have no

complaints and show no symptoms of circulatory failure the heart muscle is using up its reserve during this time. The cases which show the transient form of fibrillation do not generally need any treatment, except as is indicated by other manifestations, and in pneumonia when the picture becomes most alarming. Those who have persistent auricular fibrillation should be given digitalis to reduce the rapid heart action. There is no better drug for this purpose than digitalis, or strophanthin when more immediate action is desired.

The various means of treating heart failure were employed in these cases. All patients were put to bed, using back-rests and pillows to aid breathing if necessary. If edema was present they were given Karrel diet, consisting of 800 c.c. of milk a day, with no additional water until the edema was gone or was appreciably reduced. Mechanical removal of fluids from the body cavities was seldom necessary. One measure that is probably not sufficiently used in severe forms of heart failure is bleeding. It was customary with these patients to bleed all who showed evidence of extreme failure of the right side of the heart, i. e., marked cyanosis, pulmonary congestion, enlarged tender pulsating liver, edema, ascites, and dilatation of the right side of the heart. Frequently, with most gratifying results, 400 c.c. to 800 c.c. were removed from the median basilic vein, the relief being immediate. This would help considerably in the course of the treatment before the other measures could begin to show their effect. Although most patients were immediately given digitalis in some form, those who were not quite so urgent were sometimes allowed to go without medication for the first twelve or twenty-four hours to observe the change brought about by rest in bed. There was no fixed dose of digitalis used, but in general the patients received one gram of the powdered leaves during the first two or three days, depending on the severity of the condition. Digitalis was continued in 0.1 gram doses three times a day until a therapeutic or toxic effect was produced. In the most urgent cases strophanthin (0.0003 to 0.0005 gram doses) was given intravenously, but always only when it was certain that no digitalis had been previously given. Another helpful drug in many of the cases was theocin. Its beneficial effects as a diuretic have recently been reviewed by Christian.[15] He showed that the best results were obtained by theocin in the cardiac cases with edema who had a good kidney function, and that if given after a course of digitalis it was especially efficient as a diuretic. In all cases particular attention was paid to procuring comfortable rest during the night.

It might hardly seem necessary to emphasize the importance of following the apex-rate in conjunction with the rate of the radial

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[15] Some Studies of a Diuretic (Theocin), Arch. Int. Med., 1916, xviii, 606.

pulse in cases of auricular fibrillation. But this practice is by no means general. These two counts frequently show a marked discrepancy at first, and as the condition of the patient improves the two rates tend to coincide. In fact, it frequently happened that as the patient was improving and the apex-rate was falling the radial rate was increasing, *i. e.*, there were more beats strong enough to reach the wrist with fewer impulses arising in the ventricles. A slow radial pulse is of no significance, for it may indicate either that only a portion of the many beats are strong enough to reach the radial artery or that the heart-rate is actually slow. A slow apex-rate is always significant. In most of the cases reviewed here the heart-rate responded quite readily to the above treatment, and hand in hand there resulted an improvement in the clinical condition. There were several in whom the heart-rate was slowed without an accompanying improvement in the symptoms, and in a few neither the rate nor the clinical picture were affected.

POSTMORTEM OBSERVATIONS. All the autopsy reports of the Peter Bent Brigham Hospital for about the first three years were analyzed with special reference to the age of the patient and the condition of the heart, particularly of the mitral valve. Two hundred and sixty-one subjects in whom postmortem examinations of the heart were made (some examinations were restricted to the head or abdomen) were included in this study. Of these there were 107 over the age of fifty, or 41 per cent., and only 2 had definite chronic mitral endocarditis. One was a man of sixty years who had rheumatic fever at the ages of sixteen and fifty-five years, and at autopsy the mitral valve showed slight thickening, a ragged border of the valve flaps, and some contraction of the chordæ tendineæ. The other was a man of sixty-seven years who had rheumatic fever at the ages of forty-two and sixty years. A definite fish-mouth mitral valve was found at autopsy, although the main trouble was alcoholic cirrhosis of the liver with marked ascites. It must be stated at this point that the mitral valve is not infrequently found slightly thickened in old people with arteriosclerosis, and this is generally most prominent in the aortic cusp of the mitral valve. This to the pathologist is an indication of a degenerative and sclerotic process and not of a real inflammatory chronic endocarditis. A further postmortem finding that is met with occasionally, is small fresh vegetations on the valves which are otherwise normal. They are regarded as terminal endocarditis and seem to occur under various conditions. They do not represent any evidence of a chronic endocarditis.[16] There were 154 cases under the age of fifty years of whom 21 had definite

[16] These two considerations are generally accepted according to Dr. E. W. Goodpasture, resident pathologist at the Peter Bent Brigham Hospital.

chronic organic mitral endocarditis. This is 8 per cent. of all the autopsies analyzed and 13.6 per cent. of those under the age of fifty, In striking contrast is the fact that only 1.9 per cent. of the patients dying at an older age showed organic mitral endocarditis pathologically.

CONCLUSIONS. From a study of 128 consecutive cases of auricular fibrillation diagnosed by electrocardiograms, and of 261 consecutive autopsies the following general conclusions may be drawn.

1. Auricular fibrillation is a very common condition in a general hospital being met with almost as frequently as lobar pneumonia.

2. Syphilis plays an unimportant role in the etiology of auricular fibrillation.

3. The transient form of auricular fibrillation is much more common than is ordinarily believed. Careful observations and electrocardiographic tracings are necessary in order to avoid missing the transient cases.

4. About one-third of the cases of persistent auricular fibrillation have had one or more attacks of rheumtic fever or chorea and show clinical signs of chronic organic mitral endocarditis. The average age of these patients is about thirty-seven years. About one-third of the cases have not had rheumatic fever or chorea and show no signs of chronic organic mitral endocarditis. The average age of these patients is about fifty-eight years. About one-third of the cases fall into neither Group I or II.

5. Chronic organic mitral endocarditis is quite infrequently found in patients over fifty years of age either in the living as a result of physical examination or in the dead by postmortem examination.

6. Most patients with organic mitral disease develop mitral stenosis and only a small number reach the age of fifty years.

7. The application of these principles in the properly selected cases will aid in the diagnosis of cardiac conditions, giving particular help in the differentiation of relative and organic mitral insufficiency.

TYPHOID MENINGITIS: WITH REPORT OF A CASE.

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THE cerebrospinal and meningeal manifestations of human infection with typhoid bacillus have an abruptness of onset, a distinctiveness of symptoms, and a prognostic value which demand

unusual attention. They may also possess an importance independent of an association with the disease typhoid fever, sufficient to render unsuitable the customary designation of "complications" or "meningeal accidents." Several cases (Nos. 6, 12, 14, 16, Table II) have been reported under the caption of "primary typhoid meningitis." In all of these, except No. 14, careful necropsies serve as the basis for the statement that the meningitis was the only evidence of typhoid infection. Lavensen believes that in the instance reported by him the nasal passage was the portal of entry. While these studies are not sufficiently conclusive to set aside the older conception that the gastro-intestinal tract is the only way by which the typhoid bacillus gains entrance to the human body, nevertheless they remove the categorical element from this dictum by indicating other possible routes of infection.

Since the study of all reported cases of meningeal disease in typhoid fever, published by Cole in 1904, it has been generally accepted that the meningeal symptoms of typhoid infection may be classified in three distinct groups. These are called:

I. *Meningism.* When there are symptoms of meningitis with no demonstrable meningeal lesions and no abnormality of the spinal fluid.

II. *Serous Meningitis.* When the symptoms of meningitis are associated with non-suppurative lesions of the meninges and a spinal fluid, showing increased tension and containing B. typhosus.

III. *Purulent Meningitis.* When the meningitis is suppurative. Here the purulent spinal fluid contains typhoid bacilli.

MENINGISM. The occurrence of meningism, or symptoms of mild, transient meningeal irritation in cases of typhoid fever, is probably so common that this syndrome no longer moves the observer to record it in the medical journals. Annual reports of this condition in the literature of typhoid fever since 1904 do not equal in number the examples of so-called "meningism" seen in this hospital during the usual summer's experience with typhoid patients.

The absence of published records of this feature of typhoid fever does not, however, signify that the symptoms are not to be regarded seriously, as possibly representing an early stage of a more dangerous process. Netter has found the mortality three times as great in cases of typhoid fever showing Kernig's sign as in those which do not exhibit it. It is obvious, therefore, that on the appearance of the signs of meningitis, efforts should be made to determine the degree of the disease of the central nervous system, and means should be directed toward the relief of these symptoms. Lumbar puncture, thus indicated, is the only means of obtaining certain information as to the meningeal condition, and at the same time, as

shown by some cases, greatly improves the condition of the patient by removing spinal fluid.

SEROUS MENINGITIS. Since 1904, instances of serous meningitis have been reported by a number of authors as follows:

TABLE I.—SUMMARY OF CASE REPORTS OF SEROUS MENINGITIS IN TYPHOID FEVER.

Case.	Year.	Author.	Spinal fluid.		
			Culture.	Pressure.	Cytology.
1	1904	Achard and Paisseau	Negative	Increased	Lymphocytosis.
2	1905	Schutze	Positive	Increased	
3	1905	Schutze	Positive	Increased	
4	1908	Silberberg	Positive	Increased	
5	1908	Nieter	Positive	Increased	
6	1909	Claret and Lyon-Caen	Positive	Increased	Polys., 60 per cent. Monos. 25 per cent.
7	1910	Stein	None	Increased	Great relief after lumbar puncture in all cases.
8	1910	Stein	Negative	Increased	
9	1910	Stein	Negative	Increased	
10	1910	Schwartz	Positive	Increased	Pleocytosis with mononuclears.
11	1910	Saquépée	Positive	Increased	Monos. 95 per cent.
12	1911	Stuhmer	Positive	Increased	Typhoid bacilli seen in smears. Globulin negative.
13	1912	Lesieur and Marchand	Positive	Increased	No leukocytic reaction.
14	1914	Hannes	Positive		Cells were usually 11 per cu. mm. Globulin tests were negative.
15	1914	Hannes	Positive	Averaged	
16	1914	Hannes	Positive	130 mm.	
17	1914	Hannes	Positive	water.	

The few instances of typhoid serous meningitis seen in this clinic in the past ten years correspond to the typical cases summarized in Table I. It is seen from these observations that the spinal fluid in serous meningitis is slightly turbid, due to the mononuclear pleocytosis, and that it contains typhoid bacilli in considerable numbers. The cerebrospinal fluid in this state contains also agglutinins for Bacillus typhosus, active in dilutions as high as 1 to 100. Silberberg is of the opinion that antibacterial substances may explain the failure of organism to grow in cultures from fluids in which the bacilli are microscopically demonstrable. Serous meningitis may subside, especially after the withdrawal of the excess of spinal fluid by lumbar puncture, or it may be the early phase of a purulent meningitis. It clearly demonstrates the localization of the typhoid bacillus in the meninges. The pyogenic potentiality of the Eberth bacillus in this location is of unfavorable prognostic significance. Claret and Lyon-Caen have shown that of 13 cases of serous meningitis with typhoid bacillosis of the spinal fluid, 8 recovered while 5 died, giving a mortality of 40 per cent. of cases of typhoid fever complicated by this condition.

TABLE II.—SUMMARY OF CASES OF PURULENT TYPHOID MENINGITIS.

Case.	Year.	Author.	Sex.	Age.	History.	Autopsy.	Bacteriology.	Remarks.
1	1902	Crouchet and Buard	M	13	On 35th day of typhoid sudden onset of meningitis; purulent fluid on lumbar puncture; death 2 days later	None	B. typhosus from spinal fluid; all cultural and serological reactions typical	Not cited by Cole.
2	1905	Raymond and Sicard	M	48	During convalescence from typhoid, onset of pains in back and legs; localized purulent meningitis of lumbar cord; cured by operation	. . . .	Pure culture of B. typhosus from pus around spinal cord	Probably primary infection in lumbar vertebra.
3	1905	McCrae, J.	M	..	Death on 14th day of disease, after stupor, rigidity and convulsions	Acute encephalitis	Blood culture positive for B. typhosus	Data deficient.
4	1905	Stäubli, C.	M	22	Four weeks after beginning of typhoid, sudden onset of meningitis; purulent spinal fluid; death 20 days after meningeal symptoms began	Typical lesions of typhoid fever, with purulent cerebrospinal meningitis	B. typhosus from purulent spinal fluid	
5	1905	Delille, A.	F	9	Signs of meningitis on 21st day of typhoid fever; turbid spinal fluid with lymphocytosis at first; death 7 days later	Usual lesions of typhoid fever; thin yellow purulent exudate on meninges	B. typhosus from spinal fluid before death and at autopsy	Definite stage of serous meningitis at onset.
6	1908	Lavenson	F	26	Onset of meningitis on 10th day of typical typhoid fever	Purulent cerebrospinal meningitis; no other lesions	B. typhosus, with all typical reactions from spinal fluid before and after death	No intestinal lesions; no blood culture made; white blood cells, 20,640.
7	1908	Gurd and Nelles	M	25	Skull fractured 1 month before onset of typhoid fever; during typhoid, signs of meningitis and intracranial abscess at site of fracture	Operation: suppurative meningitis with abscess at site of fracture of skull	B. typhosus from localized cerebrospinal meningitis	B. typhosus from blood culture.
8	1908	Henry and Rosenberger	M	34	Seen on 6th day of disease after onset of meningitis; death 3 days later	Purulent meningitis; early lesions of typhoid in intestine	B. typhosus from spinal fluid by lumbar puncture	Blood contained B. typhosus.

9	1908	Southard and Richards	M	32	Patient was a paretic who had been in the asylum for 1 year; he died in coma after an acute illness of 1 week	Lesions of taboparesis; acute cerebrospinal meningitis, with polymorphonuclear exudate; no intestinal lesions of typhoid	B. typhosus from spinal fluid, brain and mesenteric lymph node	Aside from mesenteric lymphadenitis, no lesions of typhoid infection outside of the nervous system.
10	1909	Symmers and Wilson Milligan	M	37	Illness of 10 days with symptoms of serous meningitis; death on 15th day	None	B. typhosus from purulent spinal fluid after death	Widal reaction positive on 13th day.
11	1912	Lemierre and Joltrain	M	47	Meningitic syndrome on 3d day of typhoid fever; death on 5th day	Purulent cerebrospinal meningitis; typhoid ulcers in ileum	B. typhosus from meninges	Blood culture gave B. typhosus; white blood cells, 10,000.
12	1912	Lesieur and Marchand	M	41	Meningitis on 28th day of typhoid; death next day	Purulent meningitis; no intestinal lesions	B. typhosus from spinal fluid	B. typhosus from blood culture.
13	1912	O'Carroll and Purser	M	9	Convulsions on 5th day of typhoid fever and death 1 day later	Yellow pus in meninges; congestion and swelling of Peyer's patches	B. typhosus from spinal fluid before and after death	Widal positive.
14	1914	Planche and Lombard	M	21	Meningitis after 24 days of enteritis and pneumonia; death 3 days later	"Intestines absolutely normal," purulent meningitis; pneumonia	B. typhosus from purulent spinal fluid	Pneumococcus from lung; leukocytes showed 85 per cent. mononuclears.
15	1914	Planche and Lombard	M	8	Meningitis on 35th day of typhoid; death in coma next day	Typhoid lesions in intestines; suppurative meningitis	B. typhosus from spinal fluid	
16	1915	Robinson	M	55	Outspoken meningitis on 2d day; death on 4th	None	B. typhosus on repeated cultures of purulent spinal fluid	Reported as "primary typhoid meningitis."
17	1915	Ortoconi and Amenille	M	28	Soldier in French Army; stuporous until 3d day, when onset of meningitis; death next day	Purulent meningitis; ulcers in ileum	B. typhosus from spinal fluid	Borderline case between serous and purulent meningitis.
18	1915	Author's case						

As an addition to Table II might be added a case reported by Arzt and Boese, in 1908, in which it was demonstrated that B. paratyphosus was the cause of purulent meningitis in a child seven weeks old.

PURULENT MENINGITIS. A review of the literature shows that purulent meningitis due to the typhoid bacillus is both an uncommon form of meningeal disease and also a rare phase of typhoid infection. Bramwell states that the meningococcus causes 50 per cent. and the pneumococcus 42 per cent. of cases of acute primary meningitis. In addition, leptomeningitis may be caused by many organisms, as a secondary process to a focus of infection elsewhere in the body. Though no definite statistics are available, it is readily seen that after the elimination of cases of meningitis due to the tubercle bacillus, the pneumococcus, and the pyogenic cocci there remain only a few to be accounted for by the organisms of influenza, diphtheria, gonorrhea, and typhoid fever. Out of 2768 cases of typhoid fever seen in this hospital between the years 1890 and 1916, there have been 5 cases of purulent meningitis due to B. typhosus. During the same period, among the adult patients of the medical clinic, there have been 290 cases of all forms of meningitis, of which 5 were caused by the typhoid bacillus. These figures give an incidence of 0.2 per cent. for meningitis in typhoid fever and 1.75 per cent. for typhoid meningitis among the bacterial meningeal diseases. Since 1904, when Cole published a collection of 15 cases, reports of 17 additional instances of purulent typhoid meningitis have appeared. These together with the case described in this paper are summarized in Table II. In all cases included in this compilation, except Nos. 2 and 3, the identification of the typhoid bacillus in the spinal fluid has been placed beyond question by detailed cultural and serological studies.

The data furnished by these cases indicate that purulent meningitis may occur at any time during the course of typhoid infection. Aside from the cases regarded as "primary typhoid meningitis," instances are presented of the occurrence of meningitis on any day of the disease from the second to the thirty-fifth. A striking fact is the invariably fatal outcome of all cases of generalized typhoid meningitis, and that usually within three days of the onset of the meningeal symptoms. The spinal fluid in a typical case is turbid, with a yellowish tinge. Typhoid bacilli are usually demonstrable in smear preparations of the fluid, and must be found by cultures before the diagnosis can be established. While the cells of the fluid are accumulations of polymorphonuclear leukocytes, the white corpuscles of the blood are usually not much increased; rarely above 10,000. In the case reported in this paper they did not rise above 5200 per cmm. The differential count of the leukocytes has varied greatly. Planche and Lombard report 85 per cent. mononuclears in the blood of their case, while in our case there were 85 per cent. polymorphonuclear neutrophiles. The presence or absence of bronchopneumonia may have so great an influence on the blood picture that no definite conclusions can be drawn from these figures.

REPORT OF CASE. *Diagnosis:* *Typhoid fever (B. typhosus);* *purulent cerebrospinal meningitis; bronchopneumonia.*

The patient, I. J., a negress, aged nineteen years, was admitted to the medical service of the Johns Hopkins Hospital (Gen. No. 103845) on July 19, 1915. The patient was partially comatose when brought to the hospital. Her mother said that her daughter had been ill with typhoid fever for three weeks. Until the onset of this sickness the patient had never had any severe illness. For several days in the last week of June, 1915, she had had headache and dizziness. It was known on July 1 that she had fever, but she was not confined to bed until July 12, when she became prostrated and irrational. After that date a restless stupor supervened and the patient began to complain of headache and soreness in the neck.

On July 19 *physical examination* showed her to be a large, obese young negress, semicomatose, slightly jaundiced, and polypneic. Her temperature was 104° F.; pulse 132 per minute; respirations 40 per minute. The neck, slightly retracted, was painful when flexed, and Kernig's sign was slightly positive. The physical signs in the chest were those of bronchopneumonia of the lower lobes of both lungs. The abdomen was slightly distended and painful when palpated; the spleen could not be felt. The white blood cells were 5520 per cmm., with 83 per cent. polymorphonuclear leukocytes.

The signs of meningeal disease were so striking that a lumbar puncture was done at once. The spinal fluid appeared under normal pressure, was clear, watery, contained 6 cells per cmm., and gave a faintly positive globulin reaction by the Ross-Jones test. In the blood and spinal fluid the Wassermann reaction was negative, and the gold chloride reaction with the spinal fluid was normal. Cultures from the spinal fluid were negative.

On July 20 B. typhosus was grown from the blood culture and the Widal reaction was positive for the typhoid bacillus in dilution of 1 to 100. Throughout this day the patient's condition remained essentially unchanged. In the evening she became very stuporous, and a slight strabismus of the right eye appeared.

On July 21 she brightened mentally, but there was a definite divergent strabismus, slight rigidity of the neck, and absent patellar reflexes. She had been receiving ice-water sponges, and during this day her temperature did not rise above 102° F.

On July 22 her temperature rose rapidly to 103° F. She groaned continually in a restless stupor. At 10.30 P.M., with a temperature of 104° F., the white blood cells were 5200. At midnight, when her temperature was 106° F., she suddenly passed into clonic convulsions and became unconscious. There were violent jerking movements of all parts of the face, trunk, arms, and legs, and when the eyes were relatively still they showed a widely divergent strabismus. At this time her neck became readily flexible, the knee-jerks were elicited for the first time, and Kernig's sign was

no more positive than on her admission. After convulsions lasting for two hours the patient died. Lumbar puncture done during these agonal convulsions gave a turbid greenish-yellow spinal fluid under pressure of more than 200 mm. of water. The cells, not counted, formed a pavement of pus when spread on a microscopic slide. In stains for bacteria no organisms of any sort were discoverable. Cultures of the spinal fluid, however, yielded B. typhosus alone. This organism gave the typical cultural reactions of the typhoid bacillus and was agglutinated by a dilution of 1 to 3200 of the serum of a rabbit immunized with the laboratory's strain of B. typhosus. In making the cultures, varying amounts of the spinal fluid, were placed in several tubes of bile-broth and agar. Growth of the bacillus, however, occurred only in one tube. This, together, with the fact that no bacteria could be found in stained smears of the fluid, clearly indicates that very few bacilli were present, and suggests the manner in which the cause of an obscure case of meningitis might be overlooked.

Postmortem Examination. (No. 4410. Dr. R. Major. July 23, 1915.)

Summary of the Protocol. The subject was a large-framed, well-nourished negress, with slightly jaundiced conjunctivæ. Both pleural cavities were obliterated by dense fibrous adhesions. The lungs were extensively consolidated with areas of *bronchopneumonia.*

Intestine. The mucosa of the ileum near the ileocecal valve showed several round, raised, buttonhole-like ulcers, with necrotic material on their surfaces. The lymph follicles of the ileum and cecum were enlarged, and the mesenteric lymph nodes were large and soft.

Spleen. The spleen weighed 230 grams and showed the characteristic "acute splenic tumor" of infection. The liver weighed 1870 grams. The section of this organ showed extensive fatty change and areas of central necrosis. In the other organs, except the central nervous system, there were no significant abnormalities.

Brain. The meninges on the surface of the brain disclosed a considerable accumulation of yellowish-white creamy exudate. The greatest amount of this exudate was at the base of the brain, but along with the engorged bloodvessels, it continued upward over the convexity, fading out at the upper margins of the temporal lobes. The microscopic picture of this meningeal lesion corresponded with that described by MacCallum. In the arachnoid spaces and around the bloodvessels there were dense accumulations of polymorphonuclear cells. Near the pial vessels, penetrating the cortex, were a few large mononuclear cells, with inclusions in their cytoplasm, evidently the endothelial phagocytes described by MacCallum. The exudative process, however, did not affect the cortical substance of the brain. No bacteria were seen in this exudate.

SUMMARY. This report describes a case of purulent cerebro-spinal meningitis due to B. typhosus, occurring in the fourth week of a typical case of typhoid fever. The outcome, as in similar cases, was lethal within a few days after the onset of the meningitis.

Statistics of the medical clinic of the Johns Hopkins Hospital show that out of 2768 cases of typhoid fever there have been 5 cases of typhoid meningitis. Seventeen case reports of this relatively rare phase of typhoid infection are summarized from the literature on the subject. These, together with the 15 cases collected by Cole, and with the case reported herein make a total of 33 proved accounts of the condition in the statistics of typhoid fever.

From these articles are collected comparative data on the spinal fluid in meningism, serous meningitis, and purulent meningitis.

Several cases of so-called "primary typhoid meningitis" are emphasized here, since lacking intestinal lesions, the mode of infection is obscure.

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VISCERAL FINDINGS IN ONE HUNDRED SYPHILITICS.

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WITHIN the past few years our appreciation of the scope of syphilis as an etiological factor in visceral disease has been vastly widened. The routine application of the Wassermann reaction in the medical wards began immediately to direct our attention to the probability that this disease was responsible for many of the serious conditions in which it had previously been but vaguely suspected. The pathologists soon confirmed our suspicions by demonstrating the Treponema pallida in many of the suspected tissues and in some of the unsuspected. Coincidently they modified somewhat our ideas of the cellular pathology of the disease, or at least proved the syphilitic basis of certain pictures that had been considered of uncertain origin, as in the early myocardial changes of syphilis. Thus it has come about that syphilitic carditis, aortitis, pneumonitis, hepatitis, and so on have come to be comparatively common diagnoses in our medical wards.

These diagnoses are usually made, however, on very sick patients for whom far less can be accomplished than if the diagnosis had been made earlier. The source of supply of these patients seems to have received less study than the importance of the subject warrants, and the observations recorded here were made as a contribution to this phase of the subject. The syphilis clinics seemed to offer the best field for such a study, as the patients applying for treatement at these clinics usually do so because they know or suspect that they have syphilis, and not because of any suspicion that they have any visceral disease. This applies particularly to the early cases. The material in the syphilis wards at the Kings County Hospital and in the genito-urinary department of the Polhemus Memorial Clinic (Long Island College Hospital Dispensary) was kindly put at the disposal of the writer by the respective surgeons in charge, Dr. Winfield, Dr. Potter, and Dr. Fraser. I am much indebted to them and their staffs for many courtesies.

After some time spent in culling out interesting visceral lesions from this material it was decided to record also the negative findings. The work done was therefore discarded and the present series of 100 cases represents an unselected serial group in order that the frequency of the various findings might be indicated.

Of the 100 patients 22 were in the hospital, where it might be supposed that the more serious cases would be found; but as most of them merely came in for salvarsan they were not necessarily any worse than the 78 dispensary patients.

CLASSIFICATION. In order to compare the earlier with the later visceral manifestations the cases studied consisted in 50 in the secondary stage of syphilis and 50 later cases. Such a distinction is admittedly more or less artificial, but is nevertheless of some value in this connection. Patients were classified as in the secondary stage if they presented what are generally accepted as typical secondary external lesions or if they had been infected less than a year. As a matter of fact most of them were first seen as early untreated or almost untreated cases, and most of them were seen a number of times whether or not they presented pathological findings on the first examination. Patients were classified as in the tertiary stage if they presented no secondary lesions and had been infected for more than one year. The few mixed types encountered were classified as in the secondary stage. Patients in the tertiary stage were observed a number of times, so far as was possible, if they presented evidence of visceral disease. Otherwise they were not.

Eyes.—The pupils were unequal in 3 of the 50 secondary cases and in 7 of the tertiary cases. The Argyle-Robertson pupil was seen in no secondary case, but was found in 2 of the tertiary cases. They were both found to be suffering from tabes dorsalis. Exophthalmos was found in 2 early and 1 late case. All 3 were suffering from hyperthyroidism.

Thyroid Gland. Sixteen of the early and 14 of the late cases had thyroid glands which were visible and palpable. It should be stated that but two women were included in the entire series. The thyroid enlargement was well marked in 2 secondary and 1 tertiary case. It is very difficult to tell when a slight enlargement of the thyroid gland is pathological. I am quite ready to admit that the mere fact of its being visible and palpable is not proof that it is diseased, but the large proportion shown by the above figures leads one to suspect that syphilis had something to do with it. One would expect to find a larger proportion of enlarged thyroids among the earlier active than among the later ones. It can only be stated that the clinical impression gained was to the effect that the thyroids were more noticeably enlarged in the secondary cases. Measurements were not taken.

Hyperthyroidism was definitely established in 3 early and 3 late cases. In one of these the disease preceded the syphilis, but was augmented by it, and improved under antisyphilitic treatment. Of the 6 cases, 5 presented thyroid enlargement, 3 exophthalmos, 6 tachycardia, 6 fine tremor, 3 nervousness, 3 throbbing arteries; in 3 loss of weight was noticed. In a number of other patients the condition was suspected from the presence of various combinations of these symptoms, but was not considered definite enough to be included in such a statistical study. In 4 of the 6 patients the symptoms of hyperthyroidism were ameliorated by anti-

syphilitic treatment, the other 2 patients being lost sight of. The size of the thyroid was reduced in 2, the exophthalmos improved in 1 (with disappearance of v. Gräfe's sign), tachycardia in 4, throbbing vessels in 3, tremor in 1. Of the improved cases 2 were early and 2 were late. The writer has reported the case of a syphilitic woman with Graves's disease associated with transient hemolytic jaundice in which the four cardinal symptoms practically disappeared under antisyphilitic treatment.[1] Similar cures of syphilitic exophthalmic goitre have been recorded by Clark[2] and by Lewis.[3]

Lungs. No instance of syphilis of the lungs was recognized. Among the 50 early cases there were 5 who presented more or less definite evidence of pulmonary tuberculosis involving the apices. The stage of the syphilitic disease precluded a diagnosis of syphilitic pneumonitis. Considering the prevalence of phthisis it is not surprising that 5 out of 50 individuals suffering from an active debilitating infection, such as syphilis, should show signs of tuberculosis. That it was not found once among the tertiary cases suggests that those who had suffered from such a double infection had either succumbed earlier, or having passed the active stage of the syphilitic infection had overcome the other. Of the early cases seen none was of an advanced type, and none was watched long enough to determine whether the progress of the tuberculosis was unusually rapid. Among the tertiary cases there was one in whom there was definite dulness in the right back over the root of the lung, but lacking corroborative signs and symptoms a diagnosis of syphilis of the lung was not justified. There were 2 cases of emphysema in the older group.

Heart. It has been shown by Warthin[4] that the heart is a site of early predilection for invasion by the Treponema pallidum, and it is therefore not surprising there should be found considerable clinical evidence of cardiac involvement among the early as well as among the late cases. This subject has been emphasized in this country particularly by Brooks.[5] The most extensive statistical study is that of Grassmann,[6] who analyzed a series of 288 patients with secondary syphilis from the cardiac stand-point.

SUBJECTIVE SYMPTOMS. *Pain.* Of the secondary series there were 5 who complained of pain in the region of the heart or under the sternum. All 5 presented definite physical signs of abnormal cardiac conditions, which is in full agreement with Grassmann's observations on this point, the earlier observers having maintained that such symptoms were of purely functional origin.

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[1] Med. Times, December, 1915.
[2] Jour. Am. Med. Assn., lxii, 1169.   [3] Ibid., lxi, 1630.
[4] AM. JOUR. MED. SC., May, 1914.
[5] Med. Record, February 24, 1912; New York State Jour. Med., June, 1913; Interstate Med. Jour., vol. xx, No. 6; AM. JOUR. MED. SC., cxlvi, 513.
[6] Deutsch. Arch. klin. Med., lxviii, 455 and lxix, 58.

Cardiac pain was present in 4 of the late cases, and in these also abnormal physical signs were present.

Palpitation. Eight of the early cases suffered from palpitation of the heart; 5 of these showed corresponding physical anomalies. The 3 who failed to show them were not suffering from the symptom at the time when they were examined but had previously complained of it, and had been under treatment for some months since that time. One third-stage patient who was suffering from hyperthyroidism complained of palpitation.

Dyspnea. Three early cases suffered from abnormal dyspnea on exertion. It was not a very marked feature in any of the cases in this series. However, the writer has seen three months after infection a severe myocardial breakdown, with marked dyspnea and edema. In this instance a recent debauche, to which the patient was unaccustomed, had acted as a contributory factor, but was obviously not the sole cause of the disturbance. His improvement after salvarsan was in striking contrast to his previous progress. Brooks[7] has reported similar myocardial failures in secondary syphilis. One late case, with broken compensation, suffered from dyspnea.

Edema was not seen except in the case last mentioned.

PHYSICAL SIGNS. *Arrhythmia.* The arrhythmia noted so frequently by most of the older writers in early syphilis was undoubtedly of the nervous type—the sinus arrhythmia. Of course, this bears no relation to cardiac integrity and is merely evidence of a hypersensitive nervous system. In this connection it is of some interest. Fifteen of the 50 early cases studied presented wellmarked sinus arrhythmia as contrasted with the 2 of the 50 later cases who showed it. The inference is clear.

Extrasystoles, denoting a definite cardiac affection, were found but three times in the secondary series and once in the tertiary. It seems quite likely that many more examples would have been found if the time devoted to the examination of the pulse had been extended.

Auricular fibrillation was found in one late case.

Cardiac Enlargement. In studying the outlines of the heart, percussion findings were never accepted unless corroborated by palpation. A heart was not considered enlarged unless the apical impulse was definitely displaced. Enlarged hearts were found in 18 of the early cases and in 11 of the late cases.

Mitral Regurgitation. Mitral regurgitation, the presence of which could be recognized by its three cardinal symptoms, viz., apical displacement, typical murmur, and accentuated pulmonic second sound, was found in 8 early cases. Of the 8, 4 gave evidence of conditions other than syphilis which might account for

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[7] Loc. cit.

it; 1 tertiary case had a leaking mitral. It is not presumed that in any instance there was present a syphilitic mitral endocarditis. The leaks were in all probability due to cardiac dilatation.

A systolic murmur at the apex, without other signs of regurgitation, was found in 11 early and 5 late cases.

A systolic murmur at the base was found in 11 early and 6 late cases. Aside from aortitis this murmur has about the same significance as the last mentioned.

A reduplication of the second sound, most typically discernible at the apex, was found in 7 of the early cases and in no late ones. This sign is usually associated with other evidences of myocardial involvement and seems to be rather characteristic of the condition.

Throbbing carotids were seen in 6 secondary and in no tertiary cases. The heart was described as overacting in 5 early and 1 late case.

Aortic regurgitation was conspicuous by its absence. Of course, syphilitic aortic regurgitation is a common condition, but its victims usually seek relief in some medical service.

Aortitis, as signified by a rough systolic murmur transmitted from the aortic area to the neck and by a ringing aortic second, was found in 1 early and 4 late cases. The early case was a man, aged twenty-three years, who has been infected six months. There was a widened area of supracardiac dulness beside the signs mentioned above. There was a slight general arteriosclerosis, no cardiac hypertrophy, and a blood-pressure of 118 to 85. He suffered from dyspnea but had no pain. He had never been sick before. Longcope[8] speaks of syphilitic aortitis occurring six and seven months after infection. Aneurysm of the aorta was found at autopsy in one late case in the hospital series. It was situated low down behind the heart.

Arteriosclerosis occurred in 4 early and 10 late cases. The early cases averaged twenty-seven years of age and the late cases thirty-eight years. It is impossible to hold syphilis responsible for all of these cases, but the figures are strikingly suggestive.

Blood-pressure readings were made in 20 early and 20 late cases. The early cases averaged 131 systolic and 84 diastolic, while the late cases averaged 137 systolic and 87 diastolic.

Summary of Heart Findings. Of the 50 syphilitic patients in the secondary stage, 24 (48 per cent.) gave definite evidence of cardiac pathology, not always of syphilitic origin, as has been seen. This does not include those presenting merely a sinus arrhythmia, an accidental murmur, an accentuated pulmonic second sound, or such inconclusive evidence of heart trouble, which probably accounts for the discrepancy observed in a comparison with Grassmann's

[8] Arch. Int. Med., January, 1913.

figures (77 per cent); 12 of the 50 late cases showed cardiac abnormalities. Many of these, however, merely represented the hypertrophy which accompanies an arteriosclerosis.

EFFECT OF TREATMENT. Of the 14 cases of secondary syphilis with definite cardiac involvement, which were watched long enough to determine the effect of specific treatment, 11 showed improvement and 3 did not. The improvement usually amounted to a disappearance of all signs and symptoms. Possibly the 3 intractable cases would have shown improvement if watched over longer periods, although, of course, there are cases which fail to respond to all treatment.

The patients with tertiary syphilis presenting evidence of cardiac involvement, who were discovered in this investigation, for the most part presented no cardiac symptoms. The commoner physical signs, such as hypertrophy due to arteriosclerosis, would naturally not be affected by treatment, and these were not followed. One patient of the tertiary group with cardiac insufficiency had found so much relief from previous courses of antisyphilitic treatment that he had returned to the hospital a number of times, applying to the syphilitic department for treatment. The patient with aneurysm of the aorta died of bronchopneumonia shortly after admission. Only one of the patients with aortitis complained of symptoms, in this case pain, which was much relieved by salvarsan. Of the 4 patients in the tertiary stage who complained of cardiac pain, 2 were relieved by treatment and 2 were not.

Salvarsan Reaction. A peculiar cardiac reaction was twice noticed after the administration of salvarsan in early cases. This consisted in an augmentation of the signs of cardiac involvement or their appearance, such as might represent a Herxheimer reaction, except for the fact that the disturbance lasted for from two to three weeks. There was evident dilatation in both cases. A repetition of the dose was not followed by a similar reaction. This phenomena has also been noted in patients not included in this series. If the dilatation were an arsenic reaction one would expect that the individual would show the same reaction to later doses of the drug. It seems more likely that it is a true Herxheimer reaction and that the heart takes longer to recover its normal condition than do other tissues. I believe it is important that the heart should be carefully watched after the administration of salvarsan, and any signs of dilatation of the heart should be considered indications for absolute rest as long as such signs persist.

Kidneys. The kidneys were not investigated as thoroughly as they might have been. Of the secondary cases, urinalyses were made in 15 instances and albumin found in 2. One of these, an early case, was admitted to the hospital with an acute nephritis and typical secondary symptoms. He had received four intramuscular injections of mercury. The relation of the syphilis to the

nephritis is problematical.   Of the later cases the urine was studied
in 8 and was negative in all.

Suprarenals.   One case of Addison's disease of syphilitic origin
was practically cured by antiluetic treatment, and has been
reported by the writer and Dr. Schaffner.[9]

Digestive Disturbances.   Digestive disturbances were of rare
occurrence.   But one of the secondary cases complained of any
indigestion which had appeared since the infection, and that
amounted merely to a tendency to constipation and flatulency.
Of the tertiary cases 2 complained of slight indigestion and 1 of
symptoms of gastric ulcer.   This patient left before treatment
could be properly instituted.   Among the tertiary cases there
were 3 with serious stomach symptoms, and these all proved to be
the gastric crises of tabes.

The Liver.   In spite of the fact that the liver comes after the
testicle and brain in frequency of involvement (according to
Brooks[10]), the clinical manifestations of hepatic involvement are
by no means as frequent as are those of other organs.   This Brooks
ascribes to the large margin of safety which the liver possesses.
It is said that jaundice occurs in 1 to 2 per cent. of secondary
cases.[11]   This is probably due to the invasion of the liver by the
spirochetes,[12] although it is sometimes considered toxic in origin.
Brooks has demonstrated obstruction of the biliary radicles through
pressure from adjacent syphilitic periarteritis.   In the present
series 1 of the 50 secondary cases presented slight jaundice with an
enlarged and tender liver, and in 2 other patients the liver was
palpable.   Of the tertiary cases the liver in 1 was 2 inches below
the costal margin when first seen and had disappeared after two
months' treatment.   In 2 others of this series the liver was
palpable, 1 having a ptosed liver and 1 cardiac disease with broken
compensation.

Spleen.   In only 2 cases of secondary syphilis was there demon-
strable enlargement of the spleen, and 1 of these gave a history
of malaria.   These findings are radically different from those of
Wile and Elliott,[13] who noted enlarged spleens in 36 per cent. of
their cases.   Other authors whom they quote give figures varying
from about 2 per cent. to 10 per cent.   The writer has found
enlarged spleens in several cases of secondary syphilis not included
in this series, but in nothing like the proportion noted by Wile
and Elliott.   In the tertiary group an enlarged spleen was found
in one patient who gave a history of malaria.

[9] New York Med. Jour., May 27, 1916.
[10] Ibid., June 27, 1914.
[11] Editorial, Jour. Am. Med. Assn., lxi, 1633.
[12] Brooks: Loc. cit.
[13] Am. Jour. Med. Sc., cl, 512.

Nervous System. In the early cases some degree of mental perturbation and nervous hypersusceptibility was, of course, the rule. This was demonstrated physically by the frequency of nervous cardiac arrhythmias (30 per cent.). No case of definite syphilitic involvement of the nervous system was found.

In the tertiary group there was 1 case of transverse myelitis which occurred one year after infection (hospital case) and 3 cases of tabes, beside a palatal palsy of peripheral origin and a hemiplegia in a man, aged thirty-one years, coming on three years after infection.

Joints. The frequency of the occurrence of syphilitic arthropathies has been recently emphasized by Higgins.[14] In the present series 1 patient in the secondary group gave a history of pain and swelling of the fingers and knees at the same time that he was suffering from sore throat and mucous patches. All of the symptoms had disappeared during the four weeks of antisyphilitic treatment he had received at the dispensary before he was seen by the writer.

CONCLUSIONS. Visceral syphilis is at least as common and much more serious than cutaneous syphilis, which has in times past been given the greater amount of attention. The manifestations of visceral syphilis are detectable in the early stages of the disease in a large proportion of cases. Such manifestations are about as readily controlled by proper treatment as are the visible signs of the disease. It is important, however, in view of the extreme seriousness of the later stages of visceral syphilis, that the treatment be pushed energetically from the start in order to eradicate the disease while it is possible and before irremediable damage has been done. Furthermore, it is important that every patient with syphilis be carefully watched for signs of such visceral involvement as should indicate treatment beside the ordinary antisyphilitic measures. For example a dilatating heart in early syphilis indicates rest just as clearly as though it were due to rheumatic carditis, and the neglect of this precaution may leave the patient with a weak heart even though he be lucky enough to be cured of his syphilis.

Cardiac dilatation of several weeks' duration sometimes occurs after the administration of salvarsan.

To sum up, our medical wards will be deprived of their present generous supply of syphilitic wrecks only when every syphilitic patient is treated early, thoroughly, persistently, and with painstaking consideration of his individual requirements.

[14] AM. JOUR. MED. Sc., cl, 733.

PULSATING SPLEEN IN MITRAL AND TRICUSPID DISEASES.[1]

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S. S., aged sixteen years, entered Mt. Sinai Hospital in November, 1910. She had been in the hospital one and a half years before on account of chronic endocarditis, and double mitral disease with auricular fibrillation, which was rheumatic in origin.

At that time it was noted that the liver was tender and pulsating, and that the spleen was also large and tender. She left the hospital much improved; but one month later the old symptoms came back, and since then there had been more or less loss of compensation, on account of which she reëntered the hospital.

The physical status was that of advanced double mitral lesions, with tricuspid regurgitation and a moderate dilatation of both ventricles. There was also a short localized diastolic murmur over the third space to the left of the sternum. An effusion in the right chest reached the angle of the scapula. The liver extended to the umbilicus; it was hard, nodular, tender, and pulsating. The spleen was also enlarged upward and downward, and almost extended to the umbilicus. It was hard and nodular; at the tip there was a large, firm nodule. The spleen reached almost as far as the liver, but it did not touch it, as a distinct space was felt between the two organs. No note was made of pulsation of the spleen at the time of admission.

The radial pulse was small, rapid, and irregular. The veins in the neck pulsated forcibly. The polygraph showed auricular fibrillation. Systolic blood-pressure was 110 to 115.

The blood count showed 6,700,000 to 8,000,000 red blood cells; 9000 to 13,000 white blood cells; 90 per cent. polynuclears; hemoglobin 84 per cent. The urine showed a heavy trace of albumin and many granular casts.

The peculiar feel of the liver and spleen led me to suspect syphilis, although no history of it could be obtained. The Wassermann reaction was strongly positive.

It was not until the patient had been in the hospital two weeks that the pulsation was observed in the spleen for the first time. It was probably present at the time of her admission, but it was not observed. It persisted throughout her stay in the hospital. It was a distinct expansible pulsation, which was best observed on bimanual palpation, its time usually preceding that of the liver, but sometimes it seemed to coincide with it.

The course of the disease was that of any ordinary advanced

endocarditis, with an occasional infarct. She was in the hospital for a long time, and she left much improved, although when she left the fibrillation of the auricle and the pulsation of the liver and spleen were still present. Although efforts were made to trace her, she was never heard from again. This report has been delayed in the hope of observing the case again and also in the expectation of observing additional cases of pulsating spleen. However, in spite of systematic routine palpation of every enlarged spleen during the past six years I have been unable to find any additional cases.

It is to this feature of this case to which I would call attention, since this is a symptom of very rare occurrence. It was first described by Tulpius[2] in 1652. Gerhardt,[3] in 1882, reported a case in a man who had an old aortic regurgitation, and who also had malarial fever. Later on, Gerhardt[4] was also able to report two additional cases of aortic regurgitation, in both of which pericarditis with fever developed during their stay in the hospital. In both of these patients he discovered pulsation of the spleen during the febrile stage of the disease. He also noted that the increase in the size of the spleen was much greater than was usually observed under such conditions.

Prior[5] reported two cases. The first case was that of a well-compensated aortic regurgitation in which typhoid fever was contracted. The spleen only pulsated during the course of the fever. The second case was one of hypertrophy of the left ventricle, which was the result of overexertion in a workman, aged thirty-seven years. Pulsation of the spleen occurred during the course of an attack of croupous pneumonia.

Drasche[6] reported a case of pulsating splenic tumor in a female, aged seventeen years, with an advanced aortic regurgitation which had appeared during the febrile stage of an attack of croupous pneumonia. The enlarged pulsating spleen disappeared as soon as the fever was gone.

To these cases which have been collected by Litten[7] I have been able to add two additional cases, both observed by Gerhardt;[8] both of these men had aortic regurgitation and developed the pulsation of the spleen during attacks of lead colic; in both patients the pulsation disappeared as soon as the attack of lead colic was over. Fever was present in one patient and was absent in the other. In the former the liver also pulsated. No reference was made to the liver in the latter case.

[2] Quoted by Litten: Loc. cit. (7).
[3] Ztschr. f. klin. Med., 1882, Band iv, 449.
[4] Charité Annalen, 1887, Band xxii, 229.
[5] München. med. Wchnschr., 1887, Band xxxiv, 669.
[6] Wiener med. Blätter, 1888, Band xi, 1.
[7] Nothnagel's Spec. Pathol. u. Therap., 1898, Band viii, Theil 2, p. 75.
[8] Centralbl. f. klin. Med., 1888, Band ix, 1.

With the exception of the historic case of Tulpius, which he observed in 1652, all of these cases were observed within the period from 1882 to 1888. I have been unable to find any cases after this date; a striking commentary on how the careful clinical examinations have been lost since the laboratory has played such a preponderating role in the making of diagnoses.

In all of these cases the splenic pulsation was arterial and was synchronous with the cardiac systole and increased and diminished with the vigor of the cardiac action. Prior's 2 cases showed this very strikingly; in the pneumonia patient the pulsation seemed very much less during the period of cardiac weakness; and it also almost disappeared as soon as the spleen decreased in size when the fever was gone. In the 2 cases of lead colic it was only present during the period of very high blood-pressure associated with the colic.

According to Gerhardt and Litten three factors are needed: an enlarged spleen, chronic cardiac disease, and an acute febrile disease. The chronic cardiac disease always represented a marked hypertrophy of the left ventricle, usually with aortic regurgitation; only once was there idiopathic hypertrophy of the left ventricle. The fevers included pneumonia, malaria, and typhoid fever. Litten explains the phenomenon as being the result of the fever increasing the vascularity of the spleen and relaxing its tissue. As a result, the pulsation of the arteries is transmitted more readily and distinctly through the organ. This explanation does not hold in the 2 cases of lead colic. Here Gerhardt assumes that a high blood-pressure associated with the lead colic makes the pulsation in the splenic vessels more forcible.

The present case differs from those thus far reported. There was no evidence of aortic regurgitation, unless the short diastolic murmur in the third left space might be accepted as evidence of aortic regurgitation, of which, however, there was no other symptom, and there was no Corrigan pulse or double tone in the vessels; the tracings showed no sign of it; the hypertrophy of the left ventricle could easily be explained by the mitral lesion.

How can it be explained? Surely not according to Gerhardt and Litten, for most of the conditions postulated by them are absent; there was neither fever nor acute infectious disease, and there was no aortic regurgitation. There was an hypertrophy of the left ventricle and there was an enlarged spleen. The hypertrophy of the left ventricle was mitral in origin; the splenic enlargement was partly due to the cardiac disease and partly to the syphilis. There was no evidence of aneurysm or any pulsating vascular tumor.

The question at once arises whether the pulsation may not have been transmitted from the heart, liver, or aorta. This may be dismissed because the pulsation was distinctly expansile and independent of any of the other viscus. This could readily be demonstrated on bimanual examination. There were no pulsating tumors

or cysts of the spleen, and the pulsation must have originated in the splenic vessels. This was well illustrated by a series of tracings which was made by Dr. Alfred E. Cohn. The tracings include the time relations of the spleen to the liver, cardiac apex, and radial and femoral arteries. These tracings were studied by Dr. Cohn and Dr. B. S. Oppenheimer. It is not an easy task to draw con-
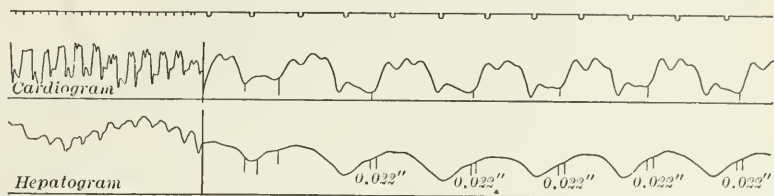
FIG. 1.—Tracings of heart and liver.
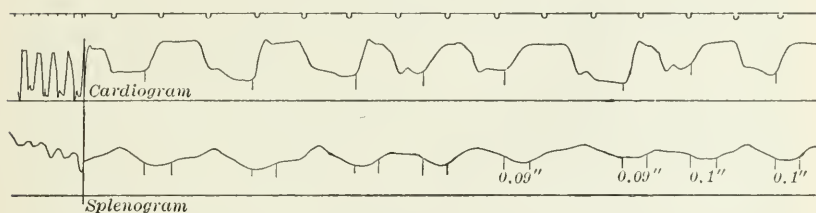
FIG. 2.—Tracings of heart and spleen.
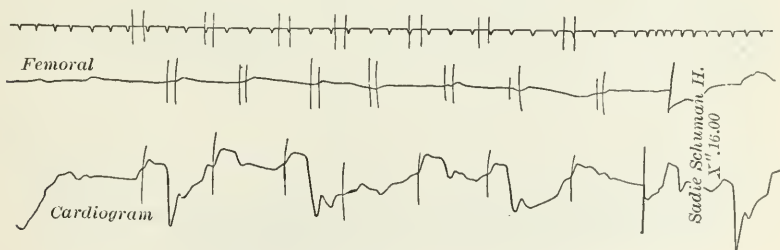
FIG. 3.—Tracings of heart and femoral artery.

clusions from them, as unfortunately no jugular or abdominal aorta tracings were made. Dr. Cohn was inclined to regard the splenic pulsations as arterial. The pulsations in the liver he considers to be of the ordinary ventricular type. Dr. Oppenheimer, after a very careful study of the tracings, is unable to reach any positive conclusions concerning the nature of the splenic tracings. He agrees

with Dr. Cohn in considering the liver pulsations to be ventricular. When two observers who have had such a large experience in interpreting tracings are unable to agree, I believe it will be wisest to simply state the findings and to leave their exact determination to the future, when possibly more cases will have been observed. The following are the time relations:

1. The cardiohepatic time is 0.022 second (Fig. 1).
2. The cardiosplenic time is 0.09 or 0.1 second (Fig. 2).
3. The cardiofemoral time is 0.1 second (Fig. 3).

These figures would indicate that the splenic pulsations are arterial, as the time relation of the femoral artery agrees so closely with that of the spleen. The dynamic conditions which exist in this case, however, do not warrant this assumption, as this conclusion would predicate the existence of an aortic regurgitation, of which there are almost no evidences. The only possible warrant for it is the short diastolic murmur in the third left space. This is not enough for a diagnosis of aortic regurgitation, all the evidence of which was absolutely lacking, although it was carefully sought for during the long period she was under observation. But even if we did assume it to be present, all the other postulates of Gerhardt and Litten are absent. To assume that the pulsation in the spleen is arterial and that that in the liver is venous is an improbable assumption. The most plausible explanation is to attribute both pulsations in the liver and the spleen to the same source, i. e., venous, for this is the type usually seen in tricuspid regurgitation. This, too, is improbable, for it is inconceivable that the propagation of the pulsations in the liver which is so closely related to the inferior vena cava should also be propagated into the splenic vein, which is a branch of the portal vein.

It is greatly to be regretted that I cannot offer any explanation of this unique case. Unfortunately, it is the only case of the kind which has ever been reported, and it was observed six years ago, when the new cardiographic methods were still in their infancy.

THE RATE OF EXCRETION OF THE THREE NITROGENOUS WASTE PRODUCTS, URIC ACID, UREA AND CREATININ IN NEPHRITIS, AS SHOWN BY COMPARATIVE STUDIES OF THE BLOOD AND URINE.

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The accumulation of the end products of protein metabolism in conditions of renal insufficiency is now a well-established fact.

Recent work in this laboratory[1] has shown that as the permeability of the kidney is lowered, this becomes evident: (1) by a retention of uric acid, (2) by that of urea, and (3) by that of creatinin, indicating that creatinin is the most readily eliminated of these three nitrogenous waste products and uric acid the most difficulty eliminated, with urea standing in an intermediate position. To obtain more definite information on this point, it has been thought worth while to compare the concentration of these waste products in the blood with their elimination in the urine. The blood and urine have, accordingly, been studied in a number of miscellaneous cases of nephritis, and likewise, for comparison, in a few individuals free from kidney disease.

A comparatively large amount of work has been done in which simultaneous determination of blood and urine urea have been made, but no work of a similar nature has been carried out with uric acid and creatinin. Considerable interest was aroused in the mechanism of the excretion of urea, following the work of Ambard and Weill[2] upon the relationship between the blood urea and the rate of urea excretion. In this country McLean and Selling,[3] McLean,[4] and Addis and Watanabe[5] have reported a large number of observations dealing with this subject.

METHODS EMPLOYED. The technic employed in the collection of specimens was almost identical with that of McLean.[6] After seventeen hours' starving, about 200 c.c. of water was given, and one and one-half hours later the collection of urine was started and a seventy-two-minute specimen collected. In patients in whom an incomplete urination was anticipated, the bladder was emptied with a catheter at the beginning and at the end of the period. In the middle of the period of urine collection, 20 c.c. or over of blood were taken.

For the estimation of the urea of both blood and urine, Van Slyke and Cullen's[7] modification of Marshall's method was employed. The Folin and Denis-Benedict[8] method for uric acid in the blood was carried out as described by Myers and Fine,[9] while for the urine the exact technic given by Benedict and Hitchcock[10] was followed. Folin's methods were used for the creatinin of both blood[11] and urine.[12]

[1] Myers, V. C., Fine, M. S., and Lough, W. G.: The Significance of the Uric Acid, Urea and Creatinin of the Blood in Nephritis, Arch. Int. Med., 1916, xvii, 570.

[2] Jour. physiol. et path. gen., 1912, xiv, 753.

[3] Jour. Biol. Chem., 1914, xix, 31.

[4] Jour. Exper. Med., 1915, xxii, 212 and 366; Jour. Am. Med. Assn., 1916, lxvi, 415.

[5] Jour. Biol. Chem., 1916, xxiv, 203; 1916, xxvii, 249.

[6] Loc. cit.

[7] Jour. Biol. Chem., 1914, xix, 211.

[8] Ibid., 1915, xx, 619.

[9] Loc. cit.   [10] Loc. cit.

[11] Folin, O.: Jour. Biol. Chem., 1914, xvii, 475.

[12] Folin, O.: Am. Jour. Physiol. 1915, xiii, 48.

Table I.—Comparative Data on the Blood and Urine in 25 Cases.

Case	Age	Date, 1916.	Sex	Blood analyses. Uric acid (Mg. to 100 c.c.)	Urea	Creat-inin	Relationship Uric acid	Urea	Creat-inin	Index of urea excretion (Mc-Lean).	Diagnostic remarks.
1-M. N.	46	June 20	M	9.2	258	9.4	2.20	2.00	0.70	0.2	Chronic interstitial nephritis; uremia. Died.
		June 23		9.1	336	9.3	...	...	...	...	
		June 27		9.1	348	10.0	1.90	1.10	0.54	3.2	
		June 30		10.0	442	12.5	1.63	1.42	2.00	0.1	
2-W. W.	30	June 9	M	4.2	145	9.6	...	0.43	...	1.3	Chronic interstitial nephritis; uremia.
		July 7		6.3	129	2.8	1.29	1.29	0.33	1.2	
3-M. C.	11	July 28	M	6.8	107	2.3	0.82	0.32	0.08	6.2	Acute parenchymatous nephritis. Improved.
		Aug. 8		7.2	93	3.9	1.10	0.32	0.13	6.5	
4-L. R.	25	July 18	F	6.0	122	10.0	1.46	2.63	1.28	0.3	Acute parenchymatous nephritis; uremia. Died.
5-J. Fi.	60	July 17	M	5.3	77	3.1	0.12	0.04	0.05	68.0	Chronic endocarditis.
		July 24		4.4	60	2.3	...	...	...	...	
6-G. A.	43	Aug. 18	M	5.5	56	3.5	0.15	0.07	0.08	42.0	Leukemia.
7-V. D.	36	July 11	M	9.3	39	2.6	0.39	0.04	0.06	77.0	Cardiac insufficiency.
		July 17		8.9	52	2.7	0.64	0.14	0.08	20.0	
		July 24		5.0	49	2.1	0.37	0.13	0.09	26.0	
		Aug. 4		6.1	40	2.1	0.47	0.12	0.09	33.0	
		Aug. 11		6.7	40	1.8	0.58	0.12	0.06	35.0	
8-E. N.	50	July 11	F	7.1	50	3.1	1.10	0.23	0.19	08.0	Probable gout; chronic endocarditis.
		June 23		5.4	29	2.4	0.20	0.05	0.10	75.0	
		June 27		4.5	37	2.7	...	...	...	...	
9-A. M.	63	June 30	M	7.7	48	2.1	0.32	0.10	0.12	35.0	Chronic interstitial nephritis; syphilitic adenitis.
		July 7		5.0	..	2.9	0.24	...	0.10	...	
		July 14		4.4	42	3.3	...	...	...	...	
10-E. P.	50	June 23	M	5.0	42	2.3	0.28	0.07	0.03	31.0	Probable hypernephroma.

Relationship between the concentration in the blood and rate of excretion. Mg. per 100 c.c. blood divided by mg. excreted per 1 hour.

Patient	Date	Age	Sex								Diagnosis
11-J. F.	July 7	40	M	6.1	39	2.9	0.47	0.11	0.14	54.0	Aortic regurgitation; hypertention.
	July 20			6.3	29	2.8	0.93	0.10	0.15	35.0	
	Aug. 1			4.6	32	2.0	0.37	0.10	0.06	65.0	
12-S. H.	Aug. 18	38	F	4.0	39	3.3	0.27	0.06	0.10	90.0	Chronic interstitial nephritis; hypertention.
	July 20			6.4	38	3.0	0.19	0.02	0.04	168.0	
	Aug. 1			4.6	24	2.2	0.17	0.04	0.03	99.0	
13-M. R.	Aug. 8	49	M	6.3	35	3.9	0.24	0.04	0.05	55.0	Endocarditis; myocarditis; chronic interstitial nephritis.
	Aug. 18			6.0	32	2.9	0.29	0.08	0.04	42.0	
	Sept. 1			5.8	32	1.8	0.26	0.08	0.02	45.0	
14-J. O.	June 20	54	M	10.0	30	2.2	0.72	0.10	0.06	68.0	Mania.
	June 30			5.1	27	2.3	0.21	0.06	0.05	75.0	
	July 7			3.3	15	3.1	0.06	0.03	0.07	250.0	
15-F. R.	July 14	22	M	4.0	28	3.9	0.12	0.05	0.08	82.0	Chronic interstitial nephritis; syphilitic adenitis.
	July 28			4.5	27	1.9	0.20	0.04	0.05	110.0	
	Aug. 8			5.6	25	4.0	0.27	0.07	0.09	74.0	
16-F. B.	Aug. 18	39	M	6.3	27	2.1	0.30	0.05	0.04	70.0	Syphilis.
17-H. B.	July 14	49	M	2.6	17	3.6	0.09	0.02	0.10	377.0	Endarteritis obliterans; arteriosclerosis.
	July 20			3.7	24	3.7	0.35	0.09	0.08	79.0	
	July 28			3.6	24	3.6	0.12	0.04	0.05	101.0	
18-S. J.	July 26	63	F	5.3	24	4.2	0.09	0.02	0.05	248.0	Chronic diffuse myocarditis; asthma.
19-R. V.	Aug. 25	60	M	4.6	23	1.5	0.16	0.07	0.02	102.0	Gastric ulcer; arteriosclerosis.
20-H. H.	Aug. 11	31	M	. . .	36	1.7	. . .	0.07	0.07	220.0	Duodenal ulcer; chronic appendicitis; constipation.
21-P. J.	July 11	60	M	4.0	29	2.3	0.18	0.07	0.08	64.0	Emphyzema; bronchitis.
	July 17			3.8	33	2.4	0.15	0.04	0.05	68.0	
	July 24			3.8	33	2.2	0.15	0.05	0.03	20.0	
22-M. D.	Aug. 4	29	M	. . .	33	1.3	. . .	0.09	0.05	74.0	Gastric ulcer.
23-H. A.	Aug. 11	25	M	4.0	30	2.0	0.31	0.05	0.04	70.0	Sciatic neuritis; neuralgia.
	Aug. 25			4.5	30	1.7	0.10	0.09	0.04	107.0	
24-W. N.	June 13	24	M	4.8	26	2.4	0.26	0.03	0.03	90.0	Probable gonorrheal arthritis.
	June 20			3.8	30	2.1	0.25	0.04	0.03	79.0	
25-J. K.	Aug. 8	62	M	2.5	18	2.5	. . .	. . .	. . .	. . .	Carcinoma of pylorus.
	Aug. 11			1.8	21	2.2	0.32	0.08	0.07	102.0	

Ambard and Weill,[13] McLean and Selling,[14] and McLean[15] have endeavored to show that there is a constant relationship between the urea of the blood and urine when simultaneously determined under certain uniform time conditions. They have worked out formulæ for the relationship of the blood urea to the urine urea, and state that the resultant of these formulæ, i. e., the combined formula (Ambard and Weill) and the index of urea excretion (McLean), is relatively constant for normal individuals, but that deviations exist in proportion to the renal insufficiency. These conclusions are not in entire harmony with our own observations, as will be pointed out at another time.

In the present paper we wish to discuss the comparative relationship of the urea, uric acid, and creatinin of both blood and urine. Fifty-five observations are recorded in 25 cases in which such determinations were simultaneously carried out, the urine specimens being collected for seventy-two minutes (one-twentieth of the twenty-four hours, as in McLean's experiments). There was some evidence of nephritis in the first 19 cases of this series, the order of arrangement being according to the descending magnitude of the blood urea. The remaining 6 cases were not regarded as cases of nephritis, and are included for purposes of comparison.

From an inspection of the blood analyses in Table I, it will be noted that there was marked nitrogen retention in the first 4 cases, 2 of the cases being diagnosed as chronic interstitial nephritis and 2 as acute parenchymatous nephritis. Case 5, suffering from chronic endocarditis, showed a blood urea quite above the normal limits, while the blood ureas of Cases 6 to 12 were likewise rather above the figures usually encountered in hospital cases not suffering from an impairment in renal function.

TABLE II.—AVERAGE COMPOSITION OF THE BLOOD FOR GROUPS OF CASES.[16]

Cases.	Impairment of renal Function.	Uric acid.	Urea.	Creatinin.
		mg. to 100 c.c. of blood.		
1 to 4	Severe	7.5	220	7.7
5 to 14	Moderate	6.0	41	2.6
15 to 19	Slight	4.4	24	3.1
20 to 25	Very slight (?)	3.7	29	2.1

A general idea of the variations found in the nitrogenous waste products of the blood in the different cases may be obtained from the average data given in Table II. It will be noted that for the average

[13] Loc. cit.   [14] Loc. cit.   [15] Loc. cit.
[16] Normal blood findings: Uric acid 2 or 3 mg., urea 25 to 35 mg., and creatinin 1 to 2.5 mg. all calculated per 100 c.c. of blood. The above figures for the normal urea of the blood refer primarily to hospital patients on a low protein diet.

data on Cases 1 to 4 the figures for all three waste products are high, although in comparison with the other cases this is especially marked for the urea and creatinin. In the second group of cases (5 to 14) it will be noted, on the other hand, that the retention is most marked in the case of the uric acid and least so in the case of the creatinin. The observations in these two groups of cases corroborate the findings of Myers, Fine and Lough. In the third group of cases (15 to 19) the figure for urea is normal, but there is an appreciable retention of both uric acid and creatinin. According to the view we have held, this would not be surprising so far as the uric acid is concerned. It is worthy of note that we have frequently found that a slight retention of creatinin occurs in syphilis, certain heart conditions, and in some advanced cases of diabetes. The figures in the fourth group of cases (20 to 25) are perfectly normal, except for a slight retention of uric acid.

A ratio has been worked out to show the relationship between these waste products in the blood and urine by dividing the milligrams of the substance per 100 c.c. of blood by the milligrams excreted per hour. From these ratios (Table I) it is evident that uric acid is much less readily eliminated than either urea or creatinin. For the urea and creatinin there is comparatively little difference, although on the average creatinin seems to be slightly more readily eliminated. This harmonizes very well with the conclusions from the determinations in the blood alone. The solubility of uric acid, even as sodium or potassium urate, is very much less than that of the urea or creatinin, and this may be the important factor in the comparatively low permeability of the kidney for this substance.

It is interesting to note in Case 1 that although uric acid was the least readily eliminated of the three waste products on the first examination, creatinin was the most poorly excreted just before death. In Case 4 it will further be observed that the urea was the most poorly eliminated.

It is believed that a general idea of this topic can best be obtained by a summary table of average figures similar to that employed in the case of the blood analyses. Such data have been collected in Table III.

TABLE III.—AVERAGE DATA ON THE RELATIONSHIP OF THE URIC ACID, UREA AND CREATININ OF BLOOD AND URINE.

Cases.	Relationship between the concentration of the nitrogenous waste products in the blood and the rate of their excretion. Mg. per 100 c.c. blood divided by mg. excreted per one hour.			Index of urea excretion (McLean).
	Uric acid.	Urea.	Creatinin.	
1 to 4	1.49	1.190	0.721	2.4
5 to 14	0.40	0.088	0.079	55.8
15 to 19	0.18	0.050	0.068	142.4
20 to 25	0.21	0.054	0.047	99.3

It will be noted that with the exception of the first group of cases (1 to 4) the uric acid was from three to four times less readily eliminated than the urea or creatinin. A comparison of the data in Groups 1, 2 and 4 would seem to substantiate the view that as the permeability of the kidney was lowered this was evident first by a retention of uric acid, later by that of urea and lastly by that of creatinin.

Ambard and Weill[17] attempted to estimate the functional ability of the kidney in normal and pathological conditions by a study of the ratio between the urea of the blood and urine. They state that they found a relatively constant ratio in normal individuals, and conclude that a deviation from this normal shows a deficiency in the function of the kidney. McLean[18] modified the formula so that the normal of his so-called "index of urea excretion" would be 100. He believed that indices below 80 showed some deficiency in the function of the kidney. The formulæ that have been used to show this relationship are given below:

Ambard's First Formula:

$$\frac{\text{Gm. of urea per liter of blood}}{\sqrt{\text{Hourly rate of excretion} \times 24 \times \dfrac{70}{\text{Kg. of body wt.}}}} = K.$$

Ambard's Second Formula:

$$\text{Hourly rate of excretion} \times 24 \times \frac{70}{\text{Kg. of body wt.}} \times \sqrt{\text{Gm. of urea per liter of urine}} = K.$$

Combined Formula:

$$\frac{\text{Gm. of urea per liter of blood}}{\sqrt{\text{Gm. of urea per 24 hrs.} \times \dfrac{70}{\text{Kg. of body wt.}}} \times \sqrt{\dfrac{\text{Gm. of urea per liter of urine}}{25}}} = K.$$

McLean's Index:

$$\frac{\text{Gm. of urea per 24 hrs.} \times \sqrt{\text{Gm. of urea per liter of urine}} \times 8.96}{\text{Body wt. in kg.} \times (\text{Gm. of urea per liter of blood})} = 100.$$

From a large number of observations made on normal individuals using the first and second formulæ of Ambard, Addis and Watanabe[19] conclude that the rate of urea excretion in man varies under physiological conditions in a manner which cannot be explained by the concentrations of urea in the blood and urine. They observed that there was a tendency to an increased rate of urea excretion to exist with higher blood urea concentrations in certain conditions in normal individuals, and that in cases with a deficiency in kidney function, there was a lowered rate of urea excretion even in the presence of a higher blood concentration. The results of Addis and Watanabe are summarized in Table IV.

[17] Loc. cit.   [18] Loc. cit.   [19] Loc. cit.

TABLE IV.—VARIATIONS FOUND BY ADDIS AND WATANABE[20] FOR THE RELATION BETWEEN THE UREA OF THE BLOOD AND URINE IN NORMAL INDIVIDUALS.

	Ambard's first formula.[21]	Ambard's second formula.[22]	Combined formula.[23]	McLean's index.[23]
Lowest . .	0.0451	27.9	0.0451	23.2
Highest .	0.1430	570.0	0.1430	355.0
Average .	0.0762	117.2	0.0762	99.6

The results obtained show such marked variations, both normally and pathologically, that it is believed that they are of comparatively little more value, either for diagnostic or prognostic purposes, than the blood urea alone.[24]

An inspection of the average data for the McLean index, given in Table III, shows that these average figures fit in very nicely with the other data. If we examine the observations as given in Table I more carefully, however, the actual practical value of the index will be found to be very small. Very low indices were found in Cases 3 and 8, but the blood creatinin was a far more reliable prognostic sign, and the same was true of Cases 7, 9, 10 and 11, with comparatively low indices.

CONCLUSIONS. From a comparative study of both blood and urine it is evident that uric acid is normally much less readily eliminated than either urea or creatinin. Although creatinin seems to be excreted slightly more readily than urea under normal conditions, there would appear to be comparatively little difference in the ability of the kidney to eliminate these two waste products.

With a lowering in the activity of the kidney the uric acid is apparently the first to suffer, although in advanced stages of nephritis the ratio between the urea of the blood and urine may be even higher than the uric acid. In these severe cases, creatinin would quite uniformly seem to be the last to be markedly influenced.

The combined formulæ of Ambard and Weill or the index of urea excretion of McLean give little more information of diagnostic or prognostic value than the blood urea alone. Furthermore, the limits of variations thus obtained are normally so great that it is difficult to define them for pathological comparison.

The author is indebted to Dr. Edward Quintard, director, and to Dr. A. F. Chace and other members of the medical department, for the opportunity to study the cases reported in this paper. He also wishes to express his appreciation to Prof. V. C. Myers, of this laboratory, for suggestions and aid in the preparation of the manuscript.

[20] Jour. Biol. Chem., 1916, xxiv, 203.
[21] Data taken from Table I.   [22] Data taken from Table III.
[23] Data recalculated from Tables I and II.
[24] This is in harmony with the more recent conclusions of Jonas L., and Austin, J. H.: AM. JOUR. MED. SC., 1916, clii, 560.

A CLINICAL STUDY OF CHLORIDE EXCRETORY FUNCTION.

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Introduction.   The purpose of this investigation has been to study the value, as a clinical test, of the method of measuring sodium chloride excretory function, recently introduced by McLean.[1]

McLean has modified the formula devised by Ambard and Weill[2] to express the laws of excretion of sodium chloride in normal individuals, so that, given the data of rate of excretion of urine, concentration of chloride in the urine and the body weight of the subject, the concentration of chloride which would be found in the blood plasma could be calculated, provided the excretory function was normal.   This modified formula is expressed as follows:

$$\text{Plasma chloride} = 5.62 + \sqrt{\frac{\text{Gm. NaCl per day} \ \sqrt{\text{Gm. NaCl per liter}}}{4.23 \times \text{body weight in kilos.}}}$$

The figure 5.62 refers to the normal threshold for chlorides, or concentration in the plasma at which excretion begins.   Ambard and Weill found that excretion began when the concentration of chlorides in the blood plasma had risen above 5.62 per liter.   The figure 4.23 is a constant introduced into the formula.

The theoretical concentration of plasma chloride calculated from the formula may then be compared with the actual concentration found by analysis of the blood plasma.   The supposed threshold of beginning excretion for any case under study may be calculated from the following formula:

$$\text{Threshold} = \text{plasma chloride} - \sqrt{\frac{\text{Gm. NaCl per day} \ \sqrt{\text{Gm. NaCl per liter}}}{4.23 \times \text{body weight in kilos.}}}$$

McLean found in a large series of examinations in normal individuals that the theoretical concentration corresponded fairly closely with the concentration actually found.   He then applied the method to the study of pathological conditions[3] and found that relatively increased concentration of chlorides in the plasma occurs especially in certain forms of cardiac and renal disease; that edema

[1] Jour. Exper. Med., 1915, xxii, 234.
[2] Semaine méd., 1912, xxxii, 217.
[3] McLean, F. C.: Jour. Exper. Med., 1915, xxxii, 366.

is usually accompanied by a relatively increased concentration of chlorides in the plasma, also that chloride and urea functions may be quite independent of one another.

The method of studying chloride excretory function hitherto most generally employed has been the test of the ability of the kidneys to excrete salt added to the diet. The patient is put upon a constant daily chloride intake until equilibrium between intake and excretion is established. Then on a certain day, 10 grams additional sodium chloride are given. If less than 85 per cent. of the added chloride is excreted within forty-eight hours it is interpreted as a retention.

Frothingham[4] studied 40 cases of chronic nephritis, comparing the test of ability of the kidney to excrete added salt with certain other diagnostic and prognostic tests of renal disease. Of the 40 cases, but one showed no impairment of ability to excrete added salt, whereas 14 excreted phthalein in normal amount. Frothingham's table shows that 9 of the cases with normal phthalein had very markedly impaired ability to excrete the added chlorides. Frothingham concluded that the added salt test is the best functional test for the detection of early chronic nephritis, but that it is of not much value in prognosis, since the ability to excrete added chloride may be greatly impaired relatively early in the course of the disease.

O'Hare[5] has studied 15 cases of nephritis by McLean's method of testing chloride excretory function and compared the results with those obtained by the Hedinger and Schlayer two-hour renal test and test of ability to excrete added chloride. He concludes that the McLean test is more satisfactory than the others.

Although the added salt test is undoubtedly of great value in the study of nephritis, it has many obvious disadvantages. The patient should be in a hospital, preferably under the care of a nurse trained specially to give metabolic diets. The test requires five or six days' time to be carried out properly. During this time all the urine must be carefully saved. If, as not infrequently occurs in nephritic cases, the patient vomits after the administration of the added salt the test is lost. Thus its application must be limited almost entirely to the comparatively small proportion of cases that can be studied in hospitals. On the other hand the method of studying excretion of chloride devised by McLean is relatively easy to carry out. It is not dependent upon any diet. It requires but two analyses. It does not necessitate having the patient in a hospital subject to the expense and loss of time incident to the added salt test. Therefore, if by the McLean test equally satisfactory information as to renal adequacy for chloride excretion could be obtained, it would be well worth adopting as a clinical test. For this reason we have tried the method in a series of cases, which have received careful

[4] AM. JOUR. MED. SC., 1915, cxlix, 808.
[5] Arch. Int. Med., 1916, xvii, 711.

clinical study and whose renal function has been tested by other methods.

METHODS. The technic of collecting specimens was carried out as recommended by McLean. The procedure was instituted usually three to four hours after the last meal. The patient was given 180 c.c. of water to drink. Thirty minutes later a seventy-two minute collection of urine was begun. In the middle of this period, blood was withdrawn and immediately shaken with a few crystals of potassium oxalate to prevent clotting. If the patient was unable to void exactly at the end of the seventy-two minute period, the period during which the urine was collected was noted to the nearest minute. The urine was measured to the nearest cubic centimeter. The blood was centrifuged for twenty minutes at high speed. The plasma was drawn off by pipette and analyzed for chloride content according to the method of McLean and Van Slyke.[6] The standard solutions were tested frequently to ensure their accuracy. Two c.c. portions of plasma were used. Nearly all the tests were made in duplicate. The urinary chlorides were determined by a modified Volhard method.

During the course of the work my attention was called by Dr. J. Harold Austin to the variability in the carbon dioxide binding capacity of plasma when no precautions have been taken to prevent escape of carbon dioxide from the whole blood. Gürber,[7] Petry[8] and others have noted that if the carbon dioxide tension of the serum were increased the cells became richer in chloride. If carbon dioxide is permitted to escape from the whole blood the plasma becomes more alkaline, so that in the mechanism of reëstablishing equilibrium of acids and bases between plasma and cells the chloride goes over from cells to plasma probably in the form of hydrochloride acid. Consequently when no attempt has been made to prevent the escape of carbon dioxide from the whole blood the chloride content of the plasma is found 0.200 to 0.500 grams per liter higher than when this loss of carbon dioxide has been prevented. The amount of migration of chloride from cells to plasma is directly dependent upon the amount of escape of carbon dioxide from the whole blood. Thus while the method of taking blood, which was recommended by McLean, is permissible for clinical determination in which small variation in threshold is not to be regarded as of great significance, a source of error is excluded by preventing the escape of carbon dioxide from the whole blood. To prevent this escape of carbon dioxide, and consequently the variable amount of migration of chloride from cells to plasma, the method of withdrawing blood under albolene, recommended by Van Slyke[9] for determination of

[6] Jour. Biol. Chem., 1915, xxi, 361.
[7] Sitzungsb. d. phys.-med. Gesellsch. zu Würzburg, 1895, 28–37.
[8] Hofmeister's Beitrage, 1902, iii, 260.
[9] Personal communication to Dr. J. H. Austin.

carbon dioxide combining power of the plasma, was used in the latter part of the work. Taking this precaution the normal plasma chloride threshold is found to be approximately 5.30 grams per liter instead of 5.62 grams per liter.

I. *Non-nephritic Group without Chloride Accumulation.* In Table I is presented a group of 10 cases supposedly without nephritis or any circulatory disturbance in the kidneys. In this group the difference between the actual and theoretical concentration of plasma chloride has varied between —0.18 and +0.12 grams per liter. McLean, in a series of seventy-two observations, found slightly greater variations.

TABLE I.—NON-NEPHRITIC GROUP WITHOUT CHLORIDE ACCUMULATION.

Case.	Age.	Sex.	Diagnosis.	Sodium chloride, grams per liter.			
				Actual.	Calculated.	Difference.	Threshold.
I	46	M.	Angina pectoris	5.87	5.88	—0.01	5.61
II	29	M.	Endothelioma of lymph nodes	5.90	5.96	—0.06	5.56
III	25	M.	Traumatic epilepsy	6.17	6.26	—0.09	5.53
IV	23	M.	Luetic aortitis	5.87	5.83	+0.04	5.66
V	63	M.	Tumor of pons	5.63[10]	5.57[11]	+0.06	5.36[11]
VI	30	M.	Gastric neurosis	5.97	6.05	—0.08	5.54
VII	26	M.	Streptococcic bacteremia	5.81	5.96	—0.15	5.47
VIII	57	M.	Chronic myocardial disease; arteriosclerosis	5.81	5.88	—0.07	5.55
IX	16	F.	Bronchial asthma	5.56	5.72	—0.18	5.44
X	57	M.	Arteriosclerosis	5.59[11]	5.47[10]	+0.12	5.42[10]

II. *Non-nephritic Group with Chloride Accumulation.* In Table II are included 8 cases which show elevated chloride threshold, although they were considered after careful study in the hospital to be non-nephritic.

CASES XI and XII.—Entered the hospital with edema, due to cardiac decompensation. On admission both showed high threshold for chlorides. After the edema had subsided the threshold returned to normal.

CASE XIII.—The chloride studies were made in this case of luetic cirrhosis of the liver, during a period when the patient had marked ascites, bilateral hydrothorax, and edema of the legs. At that time the phthalein excretion was 20 per cent. in two hours. The urine contained a cloud of albumin. Later when the collections of fluid has disappeared the phthalein rose to 60 per cent.; the urine showed only a faint trace of albumin. The retention of chlorides was probably due to circulatory disturbances in the kidneys.

CASE XIV.—Diagnosis: cardiac decompensation, secondary cirrhosis of the liver. When the chloride study was made the patient's abdomen was steadily filling with fluid. There was almost complete anuria. After withdrawal of most of the fluid a fair urinary excretion was established. Tests made at this time showed the chloride threshold very much lower.

[10] Blood taken under albolene.

CASE XV.—This case apparently belongs to the type described by Christian[11] as having disturbed salt elimination, but not, strictly speaking, actual nephritis. This man gave a history of always having eaten large amounts of salt. To test his statement a twenty-four hour specimen of urine examined for sodium chloride content while he was on the ordinary ward diet showed 29 grams. The chloride threshold was markedly above the normal on two examinations. During this time he had slight edema. He was then placed on a fixed low chloride intake and weighed every day at exactly the same time. On the day 10 grams sodium chloride was added to the diet he weighed 1.5 kilos more than on the preceding day. On that day none of the added chloride was excreted. On the following day, however, 7.9 grams extra chloride was excreted. This man has continued under observation for five months on a somewhat limited salt intake. He has shown no further tendency to edema.

CASE XVI.—This case was diagnosed as probable early renal tuberculosis. The urine never showed more than a trace of albumin. The phthalein excretion was 35 per cent. in two hours. Two c.c. indigo-carmine were injected intravenously and the ureteral orifices observed for evidence of excretion. At the end of eight minutes a faint blue stream was seen coming from the left ureter. The amount was not materially increased at the end of twenty minutes. No excretion was observed from the right ureter in twenty minutes. Therefore, whatever may have been the primary disease the case had actual renal inadequacy when these studies were made. The elevated threshold for chlorides may be considered as one of the expressions of this inadequacy.

CASE XVII.—The elevated chloride threshold in this case is difficult to explain. The urine examination, blood-pressure readings, phthalein tests, and blood urea analysis gave no evidences of nephritis. The patient was voiding only from 400 c.c. to 660 c.c. urine for several days before the first test of chloride excretory function was made. He was then given theocin, 0.2 gram three times a day for three days and the studies repeated. The plasma chloride, meanwhile, had dropped 0.5 milligram per cubic centimeter. However, the chloride threshold was still elevated above the normal.

CASE XVIII.—This case also gave no evidences of renal inadequacy. The diagnosis made was chronic myocardial disease with anginoid attacks. The statement was made by the patient's physician that there had been edema of the legs before admission to the hospital. None, however, was observed during his stay in the ward. No material change in the threshold was observed after giving theocin, 0.2 gram, three times a day for three days or after tincture of digitalis, 0.65 c.c., three times a day for five days. The only suggestive finding in this case was the fact, that the urinary concentration of chloride was always low.

[11] Christian, H. A.: AM. JOUR. MED. SC., 1916, cli, 630.

TABLE II.—CASES PRESUMABLY NON-NEPHRITIC WITH CHLORIDE ACCUMULATION.

Case.	Age.	Sex.	Date.	Diagnosis.	Edema.	Sodium chloride, grams per liter of plasma.			
						Actual.	Calculated.	Difference.	Threshold.
XI	63	M.	Oct. 26	Cardiac decompensation	+	6.25	5.86	+0.39	6.01
			Nov. 16		0	6.00	5.92	+0.08	5.70
XII	36	M.	Nov. 2	Cardiac decompensation	+	6.69	5.88	+0.81	6.43
			4		+	6.69	5.95	+0.74	6.36
			16		0	6.43	6.29	+0.14	5.76
XIII	42	M.	Nov. 21	Luetic cirrhosis	+	6.34	5.84	+0.50	6.12
XIV	67	F.	Jan. 7	Cardiac decompensation; secondary cirrhosis	+	6.65	5.68	+0.97	6.59
			Mar. 24		+	6.31	5.88	+0.43	6.05
XV	26	M.	Dec. 20	Bronchial asthma	+	6.62	6.19	+0.43	6.05
			23			6.50	5.99	+0.51	6.13
XVI	28	F.	Feb. 22	Renal tuberculosis (?)	0	6.12[12]	5.63[12]	+0.49	5.79[12]
XVII	50	M.	Nov. 8	Sciatica	0	6.81	5.95	+0.86	6.48
			18			6.31[13]	5.84	+0.47	6.09
XVIII	63	M.	Nov. 8	Myocardial weakness	+	6.37	5.84	+0.53	6.15
			18			6.31[13]	5.77	+0.54	6.16

III. *Chloride Excretory Function in Nephritis.* In Table III are presented the results of study in 22 cases of nephritis, arranged according to the clinical classification employed in the University Hospital.

Advanced Glomerulonephritis: Of 11 cases studied, 9 showed high chloride threshold. Of this group 3 cases (XX, XXIV, and XXVI) showed no lowering of chloride threshold under the influence of vapor baths and salt-free diet.

CASE XIX, whose threshold was high when the first studies were made after nineteen days' treatment with salt-free diet and vapor baths, showed a drop of 0.78 gram chloride per liter of plasma. Two days after the administration of 10 grams of sodium chloride, a slight amount of which was vomited, the threshold had again risen slightly beyond its original point. Case XXVIII, in addition to advanced nephritis, on admission had slight cardiac decompensation with edema of the legs. Under rest and digitalis the edema rapidly disappeared, but a hematuria which had been quite marked on admission, persisted. The patient was then put upon salt and protein-low diet and given a hot pack every other day. The hematuria gradually diminished until there were no macroscopic evidences of blood in the urine. Erythrocytes could still be found under the microscope, however. A McLean test at this time showed that the threshold was not raised above the normal limit. As a check upon this finding the test of ability to excrete 10 grains additional sodium chloride was made. But 4.9 grams were excreted in forty-eight hours. The urine which had been clear for about two weeks previously, on the day chloride was administered, became quite hemorrhagic in appearance. The red color gradually disappeared in the course of a week.

[12] Blood withdrawn under albolene.
[13] Had received theocin for three days.

CASES XIX and XXVIII.   These cases illustrate the point that the finding of a normal chloride threshold must not be regarded as conclusive evidence that the kidney function for chloride excretion is normal.   In Case XXVIII the sudden return of hematuria after the administration of sodium chloride suggests very strongly that the salt acted as a renal irritant.

CASE XXIX.—This patient, who had the greatest waste nitrogen retention of any case in the group, showed no accumulation of chloride in the plasma.   A test of ability to excrete added chloride could not be carried out as the patient was bordering on uremia. In this case the diagnosis of advanced glomerulonephritis was confirmed by autopsy a few weeks after the patient had left the hospital.

Thus of 11 cases of diagnosed clinically as advanced glomerulonephritis, 9 showed impairment of renal chloride excretory function by having a high chloride threshold, a tenth showed no elevation of the threshold, but impairment of ability to excrete added sodium chloride, while the eleventh, one of the most severe cases in the group, showed a normal plasma chloride, but could not be studied as to his ability to excrete added chloride.

Intermediate Glomerulonephritis.   In this group of 4 cases 2 showed a high threshold for chlorides.

CASE XXXI.—This case is of interest because the plasma chloride threshold was high, whereas the ability to excrete added salt was practically unimpaired.   On admission to the hospital this patient had advanced neuroretinitis with many hemorrhages.   The blood-pressure was 200 systolic and 110 diastolic.   The urine showed a faint trace of albumin with only an occasional cast.   The specific gravity tended between 1.005 and 1.009, but on a dry diet rose to to 1.028.   The blood nitrogen was 28 milligram per 100 c.c.   The phthalein excretion was 55 per cent. in two hours.   The plasma chloride threshold at this time was 6.44 grams per liter.   Of 10 grams added salt, 7.9 grams were excreted in forty-eight hours.   The patient was kept quietly in bed on a salt-free low protein diet.   The retinitis improved slowly.   The blood-pressure fell to 145 systolic and 88 diastolic.   Headache, which had been a troublesome feature of the case, disappeared.   The improvement has continued over a period of six months, during which time the patient has been on a restricted salt intake.

Early Glomerulonephritis.   One case, diagnosed early glomerulonephritis, was studied, as follows:

CASE XXXIV. — This patient came to the hospital, to the service of Dr. de Schweinitz, complaining of dimness of vision. He was found to have a peculiar form of proliferative retinitis, apparently not of renal origin.   Physical examination was entirely negative, except for slight enlargement of the heart to the left, accentuated aortic second sound, and slight sclerosis of the peripheral arteries.   The blood-pressure was only slightly elevated.

TABLE III.—GROUP OF NEPHRITIC CASES.

Case	Age	Sex	Date	Sodium chloride, grams per liter — Actual	Calculated	Difference	Threshold	Urine — Albumin	Casts	Specific gravity	Blood-pressure — Systolic	Diastolic	Phthalein per cent	Non-protein blood, mgr. in 100 c.c.	Blood urea, mgr. in 100 c.c.	Eye-ground examination
ADVANCED GLOMERULONEPHRITIS.																
XIX	39	F	Apr. 17 / 27	6.03[14] / 5.69[14]	5.50[14]	+0.53	5.83[14]	Cloud	Few	1.008-1.011	200 / 250	140 / 160	1		192	Renal retinitis.
XX	44	M	Mar. 6 / Mar. 26 / Feb. 25 / Mar. 4	6.03[14] / 6.25[14] / 6.22[14] / 6.22[14]	5.32[14] / 5.42[14] / 5.47[14] / 5.53[14]	-0.71 / +0.83 / +0.75 / +0.69	6.01[14] / 6.13[14] / 6.05[14] / 5.99[14]	Cloud	Many	1.010-1.012	210 / 178	135 / 120	Trace / 7		142	Angiosclerosis.
XXI	40	F	Dec. 4	6.81	5.90	+0.91	6.53	Cloud	Many	1.009-1.010	204	138	Trace		229	Neuroretinitis.
XXII	47	F	Dec. 18	6.47	5.75	+0.72	6.34	Cloud	Many	1.012-1.015	262	141	15	76	83	Angiosclerosis.
XXIII	39	M	Oct. 26	6.62	5.70	+0.92	6.54	Cloud	Many	1.009-1.013	186	115	Trace			Neuroretinitis.
XXIV	53	M	Nov. 1 / Nov. 30 / Dec.	6.19 / 6.00 / 6.02	5.64 / 5.73 / 5.65	+0.55 / +0.25 / +0.37	6.17 / 5.89 / 5.99	Trace	Many	1.010-1.012	135 / 225	97 / 165	12		96	Neuroretinitis.
XXV	35	M	Nov. 29 / Dec. 3	6.22 / 6.47	5.81 / 5.87	+0.41 / +0.60	6.03 / 6.22	Trace	Occas.	1.019-1.027	190	102	15 / 25	56	115	Disk, margins blurred; one hemorrhage. Wide-spread retinitis.
XXVI	24	M	Nov.	6.37 / 6.12 / 6.25 / 6.28 / 6.09	5.81 / 5.71 / 5.82 / 5.81 / 5.74	+0.56 / +0.41 / +0.30 / +0.44 / +0.54	6.18 / 6.03 / 5.92 / 6.06 / 6.16	Heavy	Many	1.010-1.025	242 / 178	180 / 135	33 / 37	46		Hemorrhages; neuroretinitis
XXVII	45	M	Dec. 8 / Feb. 8	5.53[14]	5.69	+0.40	6.02	Light cloud	Few	1.015-1.019	185	135	35		39	Negative.
XXVIII	34	M	Mar. 21	5.48[14]	5.43	+0.12	5.42	Light cloud	Very few	1.005-1.014	182 / 138 / 175	78 / 49 / 110	12 / 20 / Trace		80	Negative.
XXIX	34	M	Mar. 27 / 29	5.56[14]				Cloud	Many	1.009-1.011					417	Negative.
INTERMEDIATE GLOMERULONEPHRITIS.																
XXX	24	M	Feb. 1	6.41	5.99	+0.42	6.04	Cloud	Many	1.013-1.015	160	120	30		90	Neuroretinitis.
XXXI	48	F	Dec. 21	6.56	5.74	+0.82	6.44	Trace	None	1.005-1.020	200-145	110-88	55-68			Angiosclerosis.
XXXII	24	F	Feb. 16	6.62[14]	5.54[14]	+0.68	5.38[14]	Faint trace	None	1.010-1.021	190	135	35		31	Angiosclerosis.
XXXIII	39	M	Mar. 9	6.66[14]	5.55[14]	+0.11	5.41[14]	Cloud	Many	1.012-1.025	176	110	55	28	37	
EARLY GLOMERULONEPHRITIS.																
XXXIV	39	M	May 27	5.75[14]	5.46[14]	+0.29	5.59[14]	None	None	1.021	155	102	56		25	Proliferative retinitis.
CHRONIC DEGENERATIVE NEPHRITIS.																
XXXVI	29	F	Apr. 17 / 19	6.25[14] / 6.12[14]	5.62[14]	+0.63	5.93[14]	Boils solid	Many	1.023	150 / 135	110 / 90	35		36	Negative.
XXXVII	34	M	May 4	6.03[14]	5.96	+0.41	6.03	Cloud 9 gm. per liter	Many	1.028	160	90	60 / Trace		60	Old hemorrhages. Slight angiosclerosis.
XXXVIII	56	M	Jan. 22 / June 4	6.40[14]	5.33[14]	+1.07	6.37[14]	Cloud	Many	1.015				187	261	
RENAL SCLEROSIS.																
XXXIX	55	M	Nov. 27	6.12	6.02	+0.10	5.72	Faint trace	Few	1.031		130	52 / 35		48	Negative.
XL	63	F	Mar. 11	5.78[14]	5.66[14]	+0.12	5.42[14]	Cloud	Many	1.009-1.035	250					Angiosclerosis.
ACUTE PYELONEPHRITIS.																
XLI	37	F	Nov. 8	5.62	5.51	-0.11	5.51	Cloud	None	1.010-1.015	110	65	10 / Trace	187	442	Negative.

[14] Blood taken under albolene.

Numerous urine examinations failed to show either albumin or casts. The phthalein excretion was normal. There was no accumulation of urea in the blood. The sodium chloride threshold was only slightly elevated. The ability to excrete added sodium chloride was markedly diminished, but 2 out of 10 grams added salt being excreted in forty-eight hours. The degree of impairment of renal function for chlorides revealed by the inability to excrete added chlorides would scarcely have been suspected from the very slight elevation of the threshold.

Chronic Degenerative Nephritis. But 3 cases diagnosed as chronic degenerative nephritis were studied. All showed a high threshold. The chloride excretion seemed more disturbed than the phthalein or urea excretion, except in Case XXXVIII, in whom almost all kidney function had ceased.

Renal Sclerosis. The 2 cases diagnosed renal sclerosis studied, showed no retention of chloride.

Acute Pyelonephritis.

CASE XLI.—This was a case of acute pyelonephritis; the urine contained a large amount of pus and gave pure culture of Bacillus mucosus capsulatus. It is of interest chiefly because of the low chloride threshold in contrast to a tremendous retention of urea and a phthalein excretion varying from 10 per cent. to a trace. The diagnosis of acute pyelonephritis was confirmed by autopsy.

Poisoning by Mercuric Chloride.

TABLE IV.—POISONING BY MERCURIC CHLORIDE.[15]

Case.	Days after taking mercuric chl.	Sodium chloride, grams per liter.				Urine.		Phthalein percentage.	Remarks.
		Actual.	Calculated.	Difference.	Threshold.	Albumin.	Casts.		
XLIII	1	4.56	5.30	−0.74	4.56	Cloud	Many	10	Modified
	2	4.62	5.30	−0.68	4.62	"	"	25	Lambert
	4	4.92	5.30	−0.38	4.92	"	"	65	treatment.
	9	5.50	5.31	+0.19	5.49	Light cloud	None	43	8th day
	14	5.81	5.40	+0.41	5.71	Faint trace	Occasional	48	Lambert treat. dis.
XLIV	1	5.25	5.44	−0.19	5.11	Trace	"	7	Lambert
	4	5.27	5.36	−0.09	5.21	"	None	50	treatment
	9	5.87	5.46	+0.41	5.71	"	"	55	dis. 5th day.

CASE XLIII (Table IV).—White, male, age twenty-one years, weight 60 kilos. Took 0.5 gram mercuric chloride, thinking it was a headache remedy. Fifteen minutes later he discovered his mistake, took seven eggs, some starch, and milk. Brought immediately to the hospital, where a modified Lambert treatment was instituted within an hour of the time he had taken the mercuric chloride. During the first twenty-four hours he voided over 4000 c.c. of urine. For several days the urine showed enormous numbers of casts and renal epithelium and a cloud of albumin. The phthalein, which had been low, returned to normal until the Lambert treatment was

[15] All blood taken under albolene.

discontinued, when it dropped slightly again. The blood urea never rose above 0.43 gram per liter.

The concentration of chlorides in the plasma after twenty-four hours of the Lambert treatment dropped to 4.56 grams per liter the lowest figure that has been found in the laboratory. The urine at the time showed only a faint trace of chlorides, not sufficient to determine quantitatively by the McLean and Van Slyke method for chlorides. Three days later there was a slight rise in concentration of chlorides in the plasma, but still only a trace of chloride in the urine. After the Lambert treatment was discontinued and a diet containing more salt given the plasma chloride rose rapidly until there was evidence of distinct retention.

Case XLIV (Table IV).—White, male, aged twenty-four years, weight 69 kilos. While intoxicated he took 0.5 gram mercuric chloride dissolved in 150 c.c. of water. Vomited about three hours later. Then came to the hospital, where a modified Lambert treatment was instituted immediately. There was good diuresis, 3200 c.c. of urine passed in the first twenty-four-hour period. The phthalein was 7 per cent. at the first examination, but subsequently rose to normal. The urine never showed more than a trace of albumin and a few hyaline and granular casts. Highest blood urea figure 0.300 gram per liter.

The behavior of the chloride in the case resembled that of Case I. During the Lambert treatment the concentration in plasma was below the normal threshold. After the Lambert treatment was stopped there was distinct retention of the chlorides.

These cases of mercurial poisoning show how a concentration of chloride in the plasma below a normal threshold may be reached by vigorous measures of elimination. In both cases at the time the urine examinations and phthalein excretion showed most damage to the kidney the plasma chloride concentration was well below the normal threshold. Later, when the evidences of nephritis had subsided, the Lambert treatment discontinued and the patient allowed to take a diet containing salt, the concentration of chloride in the plasma quickly rose to a point where it was quite evident that there was distinct retention.

Eclampsia. Through the kindness of Dr. B. C. Hirst it was possible to study the plasma chloride in 5 cases of eclampsia and 2 cases bordering on eclampsia. Unfortunately in 2 of the cases the condition of the patient was such that accurate studies of urinary excretion could not be carried out.

The 5 cases of eclampsia all show a high plasma chloride concentration. Three in whom urinary studies could be carried out showed marked elevation of chloride threshold. In Case XLV (Table V), studied while rapid improvement was taking place, the plasma chloride fell 0.22 milligram per cubic centimeter in twenty-four hours. The two preëclamptics also showed chloride retention;

in 1 case, quite marked; in the other, which was probably a combination of preëxisting nephritis and threatened eclampsia, not so marked. This chloride retention is in contrast to the very slight tendency for waste nitrogen to be retained in eclampsia.

TABLE V.—ECLAMPSIA.

Case.	Date.	Blood-pressure.		Blood urea. Mgm. per 100 c.c.	Sodium chloride, grams per liter of plasma.			
		Systolic.	Diastolic.		Actual.	Calculated.	Difference.	Threshold.
XLV	Mar. 29	205	135	30	6.00[16] 5.78[16]			
XLVI	Feb. 28				6.37	5.71	+0.66	6.28
XLVII	Feb. 26	138	105		5.76[16]	5.36[16]	+0.40	5.70[16]
XLVIII	Feb. 3			46	6.53			
XLIX	Dec. 30	220	196	26	6.62	5.94	+0.68	6.30
				THREATENED ECLAMPSIA.				
L	May 14	180	130	44	6.00[16]	5.32[16]	+0.68	5.98[16]
LI	May 14	220	145	64	5.69[16]	5.33[16]	+0.36	5.66[16]

DISCUSSION. While the McLean method of studying renal chloride excretory function seems to give valuable information in many cases of nephritis, the results in each particular case must be regarded critically. Two cases of advanced nephritis in this series had marked impairment of their ability to excrete salt, yet the threshold at various times was found normal. On the other hand 2 cases with a very high threshold were able to sweep out added salt very efficiently. While a normal threshold does not necessarily signify that renal function for chlorides is unimpaired, a high threshold probably nearly always means impaired chloride excretion, whether this be due to actual renal disease or circulatory deficiency.

The marked effect produced by conditions interfering with the circulation in the kidney, such as passive congestion, must always be borne in mind. The threshold may be quite as high in cases of cardiac decompensation with edema as in the severest cases of advanced nephritis. The excretion of chloride is apparently far more influenced by passive congestion than is the excretion of urea.

The results of the work here presented agree in a general way with the conclusion of McLean that the chloride and urea functions may be quite independent of one another. Retention of chloride without retention of urea occurs very much more frequently than the reverse. But 2 cases were found in the series, in which there was a high blood urea figure and normal chloride threshold. Since both these cases were very ill, so that no other tests of renal adequacy for chlorides could be carried out, it is doubtful whether these cases really had good renal function for chlorides.

SUMMARY. A study of the method of investigating renal excretory function devised by McLean has been made in a series of normal and pathological cases.

[16] Blood taken under albolene.

The application of Van Slyke's method of withdrawing blood to prevent escape of carbon dioxide and the effect of this procedure upon the chloride content of the plasma were discussed.

A group of individuals with presumably normal renal function was found to conform fairly closely, in the excretion of chlorides, to the laws of excretion formulated by Ambard and Weill.

A group of cases diagnosed as non-nephritic showed elevated threshold for chlorides. Most of these cases showed evidences of circulatory disturbances in the kidneys.

Studies of chloride excretory function were made in 21 cases of nephritis, 7 cases of eclampsia and threatened eclampsia, and 2 cases of mercuric chloride poisoning.

Conclusions. 1. An elevated plasma chloride threshold, when circulatory disturbances can be excluded, is valuable evidence of the presence of nephritis.

2. A normal threshold may be found in cases with marked impairment of ability to excrete chlorides, particularly if the patient has been kept on a regime including salt-free diet and measures to stimulate elimination.

3. Sodium chloride added to the diet is sometimes excreted as completely by impaired kidneys working under the stimulation of a high chloride content of the plasma as by normal kidneys working under normal threshold; added chloride may be retained when the threshold is normal. Therefore the information gained by both methods of study is desirable,.

4. Chloride excretory function is impaired in nearly all cases of nephritis.

5. Chloride excretory function is much more disturbed in eclampsia then is urea excretory function.

FAMILIAL EPISTAXIS; A CASE REPORT.[1]

By Henry B. Richardson, M.D.,

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Osler, in 1901[2] described a "family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes." Since then he has collected from the literature and from his own experience, data on eight families afflicted with the disease.[3] Hutchinson and Oliver[4] recently reported a remarkable family, in which it occurred in three successive generations. Osler's description well sums up the disease. Its hereditary nature is particularly striking. Neither sex predominates. The attacks of

[1] From the Medical Clinic of the Peter Bent Brigham Hospital.
[2] Johns Hopkins Hosp. Bull., 1901, xii, 333.   [3] Ibid., 1907, xviii, 402.
[4] Quart. Jour. of Med., 1916, ix, 67.

epistaxis may begin in early life, and recur frequently even to advanced age, and are associated with bleeding of the mucous membranes of the mouth, sometimes of the skin as a result of trauma, and possibly of the gastro-intestinal tract and lungs. The telangiectases, though occurring chiefly in the mucous membranes of the mouth and nose, may appear over the body surface in general, particularly on the trunk and hands. The anemia produced is of a pronounced secondary type. The blood coagulation time is normal. In these several papers[5] the literature of the subject is given in sufficient detail to warrant its not being discussed again.

CASE I.—C. S. was admitted to the medical wards of the Peter Bent Brigham Hospital on January 28, 1916. He is a German, born in Germany, aged fifty-three years, and has lived in this country for twenty-eight years. The father died of apoplexy when the patient was four years old. The mother suffered from epistaxis, though never to such an extent as the patient. She died of an operation during childbirth. Of the four other children, two boys died in infancy, at the ages of six and eighteen months. A brother and sister were still living and well when last heard from, though the latter also was subject to bleeding from the nose, less severe than that of the patient. Each of these had a daughter, of whom nothing is known as to epistaxis or spots. A maternal cousin was known to have spots on her face, and to be subject to epistaxis, and her two sons and two daughters were all subject to epistaxis. Further details of the family's history are unfortunately missing, as no response was received to letters of inquiry sent to Germany.

The patient married twice. Of the two sons by the first marriage in 1888, the elder is free from symptoms, but the younger, recently married, is subject to epistaxis (Case II). The patient's first wife died four years ago. In 1913 he married again, and has one child, a year old, who so far has had no nosebleeds. The patient is a teamster on an express wagon, working eight or nine hours a day, and doing much heavy lifting. He is accustomed to taking one or two bottles of beer daily, a cup of tea and a cup of coffee, but rarely smokes. He has had no illnesses, except an occasional mild sore throat, and a history of "kidney trouble," four years previous, for which he was treated by a private physician. He denies having had venereal disease.

Symptoms of the present illness began at least ten years ago, when spots were noticed on his face. These have been constantly present though varying in number, and have showed a tendency to bleed slightly if scratched. About four years previous to his admission he became subject to exhaustion, dizziness, pallor, and yellowness of the skin. This condition increased in severity. The attending physician is said to have noticed that the scleræ were yellow. The

⁵ Osler: Quart. Jour. of Med., 1907–08, i, 53; Parkes Weber, Lancet, London, 1907, ii, 160.

patient then began to have left temporal headache, relieved by spontaneous discharge from the ear. Nevertheless, he continued weak for three or four months, and his weight dropped from 150 to 135 pounds. His health then improved and remained good until about a year ago, when he first had a hemorrhage from the nose, "als ob ein Vieh geschlaetet werde," which he estimated at about one quart in amount, followed by marked weakness, pallor, and vertigo. After six or seven weeks he again recovered and felt well and strong, with the exception of a left lateral headache, until nine days before admission. Then he had another profuse nasal hemorrhage, estimated this time at about one pint, and became weak and pale. Bleeding recurred each time that he blew his nose, but was not so severe. Shortly after the hemorrhage he noticed tarry stools. Both of his severe hemorrhages have occurred in winter, and he has noticed a tendency to bleed on the colder days of all seasons. He has never bled abnormally from cuts. He entered the hospital without further change in condition.

The physical examination showed him to be a well-developed, powerfully muscled, and intelligent German, past middle age, and in no obvious discomfort. The face is pale and has an orange-yellow tinge. On it are numerous, irregularly distributed, cherry-red areas, averaging about 2 mm. in diameter, the border of many of which is formed by a close network of serpentine lines. On pressure the color disappears for an instant. These are most numerous in the region about the mouth and nostrils, particularly the cheeks, and on and just below the lower lip. (This facial distribution of telangiectases strikingly resembles that in one of Osler's patients, of whom a colored drawing is reproduced in Osler's paper in the *Quarterly Journal of Medicine*). There are many smaller areas above and close to the eyebrows. There is a moderate yellowish pigmentation of the palate, on which a few red patches similar to those on his face are visible, as well as two or three on the buccal mucous membranes. On the right side of the nasal septum, about 2 cm. from the nares, is an area 5 to 10 mm. long, bright cherry red in color, consisting of three elongated patches. Beside this is a white area, suggestive of scar tissue. On the left nasal cavity are several small blood clots, and on the septum there is a circle of red nodular elevations, with a shallow depression in the center. Rhinoscopy, by Doctor C. B. Walker, disclosed numerous lesions of this type on the septum and turbinates.

The trunk and lower extremities are clear, but on the dorsum of the right finger there is a red area about 1.5 mm. in diameter, with sharply defined borders which disappear on pressure. Under three of the nails are similar minute areas. On the glans penis are two more, but these cannot be pressed out. The left testicle is enlarged. Transillumination showed the enlargement to be a hydrocele. There are no herniae, although the hernial rings are slightly enlarged.

Ophthalmoscopic examination failed to show hemorrhage or other abnormalities of the retinæ. Examination of the circulation was essentially negative, except for a slight enlargement of the heart to the left, a blowing systolic murmur best heard at the pulmonary area, and a moderately increased arterial pulsation. The blood-pressure was 80 systolic, 36 diastolic.

The blood showed a well-marked secondary anemia, the hemoglobin being 55 per cent., the erythrocytes 3,400,000. The white count was 9300. The smear showed 70 per cent. of neutrophiles, 10 per cent. of small mononuclears, 13 per cent. of large mononuclears, 3 per cent. of eosinophiles, 1 per cent. of basophiles, and 3 per cent. of transitional cells. The erythrocytes showed poikilocytosis and anisocytosis. The coagulation time as measured in a single glass tube was four minutes. The urine contained at first the slightest possible trace of albumin, then a large trace, but none on three subsequent examinations. Neither erythrocytes nor casts were found in the urine on any of five examinations. Gastric analysis demonstrated a hydrochloric acid deficit in each of three specimens, withdrawn at intervals of three-quarters of an hour after the Ewald test-meal by means of a Rehfuss tube. The Wassermann reaction, at first "plus minus," was later reported negative.

On the night of January 29, the patient lost a small amount of blood from the left nostril, and again on the following day, but not enough to soak a handkerchief. On January 31 the administration of saccharated ferrous carbonate 0.25 gram, three times daily, was begun. The patient continued to have slight hemorrhages from the left nostril up to two days before discharge. On February 7 the administration of calcium lactate, 1 gram four times daily, was begun, to be continued in the outdoor department. He was discharged on February 11, feeling better and stronger, but with no marked objective change, except an increase of 1,000,000 in the erythrocyte count. He visited the outdoor department at intervals and received prescriptions for iron and calcium lactate, the latter in decreased doses. He continued to have slight hemorrhages from the left nostril, and on one occasion small clots were found in the right. The hemoglobin gradually increased. On June 9 it was 72 per cent. (Sahli), and the erythrocytes numbered 4,800,000, an increase of 500,000 since discharge. The smear was normal, except for a marked achromia. The differential count showed normal relations as opposed to the low percentage of small mononuclears observed in the hospital. The leukocyte count was 5800, the blood-pressure 132 systolic and 81 diastolic, the urine entirely negative. The left border of the heart was normal and the systolic murmur had disappeared. There was no marked change in the telangiectases. The patient looked strong and healthy, and was again doing heavy physical work.

CASE II.—R. S., aged twenty-five, younger son of the above, visited the outdoor department of the Peter Bent Brigham Hospital

on June 28, 1916, on request. He has been married for two years, having no children. His wife is in good health, but has had one recent miscarriage. He is a traveling salesman and undergoes no heavy exertion. His habits are excellent. He had measles in childhood, but has always been strong, except for a susceptibility to sore throats and colds. He has been able to play baseball and football at a preparatory school, and later on a university team. He denies having had any venereal disease.

Ever since he can remember he has had frequent epistaxis, averaging two or three times a week, and seven times during the last two weeks. The hemorrhages come from either nostril. Twice, an attack has consisted of a gush of blood, though usually they are less severe, and have always been readily controlled within two or three minutes by application of ice-water to the nose. They sometimes have come without obvious cause, but usually as a result of slight trauma or sneezing. He has often noticed that change of temperature, as in entering a hot boiler room, precipitates an attack. His wife has remarked on a blotchy appearance of his face, but he has never noticed spots there or elsewhere, except for a minute one on the upper arm. He has never bled freely from cuts.

A general physical examination shows an excellently developed man of good musculature, though slightly obese and flabby. The findings were negative except for the condition of the skin. On the left side of the nose, are two minute thread-like telangiectases of a radial arrangement. On the cheeks, under the melar bones, there is a slight telangiectatic enlargement of the finer vessels. This is also seen in the ears, especially in the fossa of the helix, and in both cases can be largely or entirely pressed out. On the end of the tongue is a round pink depressed area, about 1 or 2 mm. in diameter, and not affected by pressure. Rhinoscopy, by Dr. C. B. Walker, was negative, showing no telangiectases. On the skin by the right little finger nail is a minute cherry-red area, and similar ones under the third and fourth finger nails of the left hand. All these are blanched by pressure. There is a minute angioma on the right upper arm. No telangiectases are visible elsewhere.

The urine contains no sugar, albumin, erythrocytes, or casts. The blood-pressure is 122 systolic and 68 diastolic. The coagulation time as measured in a single glass tube is seven minutes. The hemoglobin by Sahli's method is 123 per cent. The erythrocytes number 6,700,000, the leukocytes 10,000. In the smear the erythrocytes are normal, as is also the differential count of the leukocytes. No abnormal types of cells are seen.

The interest in these cases lies mainly in their familial occurrence. As a symptom the epistaxis is very annoying to the individual and not infrequently serious owing to the severe secondary anemia that incapacitates. These families with hereditary multiple telangiectases associated with epistaxis are rare enough to justify this brief record of an additional family.

DIAGNOSIS OF EARLY PULMONARY TUBERCULOSIS.[1]

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THE recognition of early pulmonary tuberculosis belongs rather to the physician in general practice and to the internist than to those who devote their whole professional time to the care and management of tuberculous patients. Active tuberculosis is the only form that concerns the clinician, and is the only one of import to the patient. This fact, emphasized by Baldwin a few years ago, has not been fully appreciated by the profession. Early pulmonary tuberculosis, like the diagnosis of most chronic diseases in their early stages, cannot be made at one seance with the patient. Pulmonary tuberculosis which can be positively diagnosed at the first examination is one of established pathology and probable permanent damage. One must realize then at the outset that the diagnosis of this disease in its early stages, when amenable to cure, is very often a difficult problem, and its importance makes the time spent on solving this problem for a patient well worth while. When the problem is solved it is not only fair but absolutely essential to tell the patient whether or not the disease exists, because upon his coöperation depends the curability more than in any other disease. The chief complaint which these cases present is frequently suggestive of something remote from the seat of pathology. Epigastric pain, fatigue, loss of weight, palpitation, flushing, malaise, as well as the common ones of cough, fever, asthenia, or expectoration are among those offered by the patients. As in chronic diseases of the stomach and intestinal tract a study of the history of these cases is of prime importance. A definite knowledge of tuberculous association is of far more significance than that of diseased ancestry. An attack of pleurisy, especially if accompanied by effusion, is highly indicative of tuberculous potentiality. The identification of some local focus, either in the tonsil or cervical glands, is a possible indicator of the damaging infection in the lung.

An inquiry which elicits from the patient hemoptysis, even of the slightest degree, while not pathognomonic of tuberculosis, is a fairly accurate sign and deserves analysis. Again, analogous to the study of carcinoma, syphilis, and leukemias a history of great loss of weight without apparent cause to the patient, particularly with some or all of the foregoing factors, justifies suspicion of pulmonary tuberculosis. A brief record of the day's work and life and symptoms of such a patient during his waking hours deserves the utmost

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[1] Read before the Westmoreland County Medical Society, Pennsylvania, April 4, 1916.

cognizance. The examination of the patient himself presents two aspects: (1) the physical, which up to the present time is still the more valuable, and (2) the laboratory, which is an important accessory and may in the future supersede the physical. The physical examination includes a prolonged study of recorded temperatures, weight studies under forced feeding, and repeated examination of thorax with recorded areas, the seat of rales. The laboratory examination comprises tests of the sputum, skin, blood, roentgen-ray findings, and the complement-fixation. In making observations of temperature study it is my own practice to supply the patient with an ordinary filing card, upon which definite hours are marked at which he is to take his temperature and record it. This is kept over a period of ten days, when he returns his card for my observation and analysis. At the same time he is placed on a mixture of milk, cream, and eggs, the equivalent of at least 1000 calories, which is added to his ordinary general diet. Also, his weight is noted before carrying out this plan and at its completion.

During this period of diagnostic study the patient is instructed to continue his ordinary occupation and in no way to modify his mode of living. The usual methods of physical diagnosis are carried out next to the naked thorax and a careful record made of suspected pathological findings. This is particularly true of voice transmission and the presence of rales. The so-called latent rale is diligently sought for and their location recorded and marked on a graphic figure.

At the second and subsequent examinations, should they be necessary, these locations and the presence of rales are carefully compared and checked up with former findings. Persistent slight rise in temperature, especially in the late afternoon, at the time of greatest fatigue, with increased pulse-rate, which should be observed at this time; no satisfactory gain in weight under the forced feeding; the presence of rales and particularly the latent rale in the same area formerly observed, spells presumptively early pulmonary suberculosis.

Sputum analysis, while always desirable, is really not a true factor in the early recognition of this disease, because its absence is not conclusive negative evidence and its presence usually denotes established tuberculous infection, with damage. The various skin tests, either the cutaneous or intracutaneous, as introduced by von Pirquet and others, have two values: (1) in the examination of children under eight to ten years of age, and (2) as a preliminary test to the subcutaneous tests as practised on adults. The eye test, or Calmette test, has fallen into disuse because of dangers to the eye; but some clinicians believe in its revival, as it has a greater prognostic interpretation than any of the others. Ordinary blood counts have comparatively little significance, although the presence of a slight leukocytosis of 10,000 to 12,000 is found in tuberculosis,

malaria, and carcinoma, and while differential counts show increased lymphocytosis, a condition which may also be present in syphilis. It was the hope of the roentgen-ray worker that by the fluoroscope and the plate early active tuberculosis could be readily solved. This has proved a chimera, because while the damaged lung is often apparent in its diseased parts on the plate, its activity can in no way be designated nor recognized. The fluoroscope, while showing the movement, is of little value in determining early pathological activity.

In this country the complement-fixation test for tuberculosis has best been presented by Craige, of the United States Army. This test in its technic is analogous to other complement-fixation tests, the most familiar of which is the Wassermann test for syphilis. This reaction is not only of value in suspected cases in which no physical signs are present, the best cases for cure, but also shows that cases which are considered in a state of cure are not entirely free from infection as long as this test is positive. The great value in this study along these lines is the fact that heretofore so-called cured cases will be handled better and longer and the ultimate results will be much more lasting.

Purposely, there has been avoided in this brief paper all the stereotyped signs and symptoms, which in text-books are attributed to this disease. They almost all stand for established tuberculosis. Incipient tuberculosis, much better called early tuberculosis, and the cases most hopeful of cure may require all the foregoing studies before arriving at a definite diagnosis; but so much depends on the proper solution of these cases, from a sociological point of view as well as industrial and economic aspects, that it is incumbent upon us not to treat these lightly or carelessly.

Some conclusions are: (1) the diagnosis of early curable tuberculosis is difficult at times; (2) suspicious cases should, if possible, be worked out to a confirmation by all means available; (3) the only tuberculosis of the lung that concerns us is active tuberculosis; (4) such diagnosis is best made by the general medical man; (5) an immediate diagnosis is sometimes impossible, and a statement made to the patient that you can find no active tuberculosis is an honest one, no matter what subsequent developments may occur.

THE INFLUENCE OF RENAL FUNCTION ON HYPERGLYCEMIA AND GLYCOSURIA IN DIABETES MELLITUS.

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(From the First Medical Service, Mount Sinai Hospital.)

The role of the kidney in the production and regulation of glycosuria still remains an unsettled problem. It is generally conceded that the presence of sugar in the urine usually represents an overflow from the blood. This assumption presupposes that the quantity of sugar in the blood is in excess of what the kidneys can tolerate or utilize, thereby causing its excretion. The point at which sugar begins to appear in the urine (threshold value) has not been definitely established. Numerous attempts have been made to ascertain the exact blood-sugar level which leads to glycosuria by means of oral and intravenous administration of glucose, but the results obtained thus far are not concordant. It is certain, however, that the kidneys of a normal individual are usually quite "impermeable" for the quantity of glucose that circulates in the blood even after the ingestion of large amounts of carbohydrates.

INCREASED RENAL PERMEABILITY. Certain instances of glycosuria are on record in which an increase in the blood-sugar content above the normal percentage was not present, or rather not demonstrated. These cases have been variously termed "renal diabetes" or "renal glycosuria."[1] The phenomenon revealed by them is usually explained on the basis that the kidneys are more permeable to sugar than normally. In the light of recent work by the author,[2] the evidence adduced in proof of the existence of a renal diabetes or renal glycosuria cannot be regarded as wholly sufficient. It is yet to be determined that in these forms of glycosuria the "percentile" sugar content is the proper index of the actual amount of sugar in the blood.

The results of the investigation referred to point to the probability that the total sugar content of the blood plays the leading part in determining the presence or absence of a hyperglycemia and not its percentile concentration. According to this conception a hyperglycemia (increase in the total sugar content) may be present without showing any increase in the percentage of the blood-sugar. Because of this fact a glycosuria may even occur when the sugar content is apparently not increased. These phenomena appear in certain cases

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[1] Lewis, D. S., and Mosenthal, H.: Johns Hopkins Bull., 1916, xxvii, 133.
[2] Epstein, Albert A.: Proc. Soc. Exp. Biol. and Med., 1916, xiii, 67; also, Relation of Hyperglycemia to Glycosuria, Monograph, May, 1916, New York.

of diabetes mellitus, and the following protocol is offered as an example.[3]

CASE HISTORY.—G. R.; female, aged forty-two years; admitted to the hospital (service of Dr. N. E. Brill) November 18, 1914. Chief complaints of patient: pruritus vulvæ, weakness, loss of weight, polydipsia, and polyuria. Exact date of onset of symptoms not known; but pruritus developed in summer of 1914, lasted a short time, and recurred two months prior to admission to the hospital. The polydipsia and polyuria were noted one month before the return of the pruritus.

Upon physical examination the patient appeared poorly nourished, with cheeks flushed, skin dry, and lips and tongue parched. A distinct acetone odor to the breath was present. Chest examination revealed the presence of a chronic bronchitis. Heart action was poor; no other cardiovascular phenomena. Abdomen lax; liver palpable below free border of ribs on deep inspiration. Marked redness of the vulva and the parts about. Cervix lacerated; uterus enlarged.[4]

On a mixed hospital diet the patient's urine contained from 2.1 to 4.2 per cent. of sugar, containing between 22 and 30 grams of glucose daily.

November 23, 1914, the blood-sugar and the relative blood volume were determined in the morning on a fasting stomach. Directly thereafter the patient was given a test breakfast of 50 grams of glucose in 200 c.c. of coffee. The blood-sugar, relative blood volume, and the urine were examined hourly for a number of hours. The results obtained are tabulated below.

TABLE I.

| Time. | Blood-sugar, per cent. | Urine | | |
		Quantity, c.c.	Sugar, per cent.	Total sugar, grams.
9.30 A.M.	0.152			
10.30 A.M.	0.264	142	5.71	8.11
11.30 A.M.	0.184	62	5.45	3.38
12.30 A.M.	0.164	33	4.00	1.32
1.30 P.M.	0.116	17	1.54	0.26
2.30 P.M.	0.122	14	2.25	0.32
3.30 P.M.	0.138			

On a restricted diet the glycosuria disappeared very rapidly and the blood-sugar dropped to normal. The patient's general condition improved and the symptoms originally complained of were no longer present. The above test was repeated on December 2 and the following results were obtained.

[3] Epstein, Albert A.: Loc. cit.
[4] It was discovered subsequently that the patient was in the fifth week of pregnancy when she entered the hospital.

TABLE II.

Time.	Blood-sugar, per cent.	Urine		
		Quantity, c.c.	Sugar, per cent.	Total sugar, grams.
9.30 A.M.	0.080			
10.30 A.M.	0.121	47	0.30	0.141
11.30 A.M.	0.140	58	3.04	1.763
12.30 A.M.	0.125	47	4.36	2.049
1.30 P.M.	0.095	12	1.37	0.164
2.30 P.M.	0.076	25	0.30	0.075

The results yielded by the second test are of unusual interest and importance. It appears that the administration of the glucose in the test breakfast gave rise to an intense glycosuria, although the blood-sugar remained practically normal throughout the period of observation. At least the course pursued by the glycemia at this stage of the disease is comparable to that observed in cases of "renal diabetes."

After the subsidence of the glycosuria caused by the test there no longer appeared any sugar in the urine, although the diet was steadily made more liberal. The patient's condition continued to improve. On December 19, when the patient appeared to be in very good health and capable of tolerating liberal amounts of carbohydrates, another test similar to the one above was made, with the object of ascertaining the reaction of the blood and the kidneys to the administration of glucose. The results of this test appear in the table below.

TABLE III.

Time.	Blood-sugar, per cent.	Urine		
		Quantity, c.c.	Sugar, per cent.	Total sugar, grams.
9.30 A.M.	0.073			
10.30 A.M.	0.067	34	0	
11.30 A.M.	0.114	32	4.00	1.260
12.30 P.M.	0.127	98	4.36	4.273
1.30 P.M.	0.085	60	5.33	3.198
2.30 P.M.	. . . . .	52	3.43	1.783

We observe here that the patient's blood-sugar on a fasting stomach reaches a low level, 0.075 per cent. No hyperglycemia is in evidence at any time during the entire test, at the same time that a very pronounced glycosuria is present.

I know of no case of "renal diabetes" in the literature in which so marked a glycosuria is present associated with so low a blood-sugar content. Without a definite knowledge of the antecedent history of this case, and the facts gleaned from the earlier tests, one might regard the case at this stage as an instance of "renal diabetes" or "renal glycosuria." The fact that the ingestion of glucose caused the glycosuria would not necessarily disbar it from this classification. The important feature is the absence of a hyperglycemia. If then the percentile blood-sugar content could be taken as the true index of the amount of glucose present in the blood the conclusion would be

warranted that the kidneys of this patient were or had become unusually permeable to sugar.

However, that the absence of hyperglycemia in the second and third tests made on this patient is only apparent and not real is evident from observations made on the blood volume simultaneously with the blood and urine analysis for sugar.[5]   The data obtained show that the blood volume had become much increased, and, although the percentage concentration of glucose is low the total amount in circulation is increased throughout the glycosuric period. The increase in the blood volume that had occurred while the patient was under observation is demonstrated by the following results.

TABLE IV.—SHOWING CHANGES IN THE RELATIVE BLOOD VOLUME ON THE THREE TEST DAYS.

	Blood plasma, per cent.			Blood cells, per cent.			Relative bloo1 volume, per cent.		
	Nov. 23.	Dec. 2.	Dec. 19.	Nov. 23.	Dec. 2.	Dec. 19.	Nov. 23.	Dec. 2.	Dec. 19.
9.30 A.M.	48.3	55.1	57.5	51.7	44.9	42.5	100.0	115.2	121.6
10.30 A.M.	51.8	55.2	60.9	48.2	44.8	39.1	107.4	115.2	132.2
11.30 A.M.	53.9	53.2	59.7	46.1	46.8	40.3	112.2	110.6	128.2
12.30 A.M.	53.8	56.3	59.9	46.3	43.7	40.1	111.9	118.6	128.9
1.30 P.M.	53.8	56.0	58.3	46.2	44.0	41.7	111.9	117.5	123.9
2.30 P.M.	56.2	56.0	59.7	43.8	44.0	40.3	118.0	117.5	127.7
3.30 P.M.	54.6	56.3	..	45.5	43.7	..	113.9	118.6	...

These data show very clearly just what has taken place in the circulating blood.   Evidently its volume had increased, so that on December 2 and 19 it was found to be decidedly greater than it was at the time of the first examination on November 24.   The percentages of sugar found in the blood upon examination are therefore masked by the alteration in the blood volume.   Had the blood volume remained unchanged the blood-sugar content would really have been as follows:

TABLE V.—SHOWING THE CORRECTED BLOOD–SUGAR CONTENT ON THE THREE TEST DAYS.

	Blood-sugar		
	Nov. 23. Per cent.	Dec. 2. Per cent.	Dec. 19. Per cent.
9.30 A.M.	0.152	0.092	0.088
10.30 A.M.	0.283	0.134	0.089
11.30 A.M.	0.206	0.166	0.146
12.30 P.M.	0.183	0.147	0.164
1.30 P.M.	0.130	0.112	0.108
2.30 P.M.	0.144	0.090	
3.30 P.M.	0.158		

[5] The blood variations were determined by means of the simplified hematocrit devised by the author (Jour. Lab. and Clin. Med., 1916, i, 610).

According to my understanding of a hyperglycemia (*i. e.*, increase in the total blood-sugar content[6] these figures represent a definite hyperglycemia, and are compatible with the findings in the urine in the corresponding periods of time.

If we disregard the blood volume changes and their influence on the blood-sugar content in this instance we must draw the conclusion that the kidneys had become more permeable to glucose than they were at the outset, or that they had acquired the ability to eliminate sugar in the absence of a hyperglycemia. (Compare Tables I, II, III.) We would thus have a condition resembling renal glycosuria in a truly diabetic individual.

George Graham[7] records one case of definite diabetes with a relatively low blood-sugar content, and terms the condition "low-level leak-point." This observer, however, has made no control estimations of the blood volume in his case, and hence the interpretation given cannot be accepted as conclusive.

The occurrence of a glycosuria of purely renal origin is, of course, quite possible; but with the evidence which we possess concerning the phenomenon it seems premature to speak of the existence of "renal diabetes" or "renal glycosuria," or to regard the cases recorded in the literature as definite instances of increased renal permeability for glucose.

It appears fairly certain that changes in blood volume occur and that these changes exert an influence upon the concentration of different ingredients. It will therefore be necessary in the future in a consideration of the subject of hyperglycemia to take variations in blood volume into definite account. With the methods which we now possess for estimating blood-sugar and determining the blood volume there ought to be no difficulty in ascertaining whether or not a "renal glycosuria" or "diabetes" represents a condition of increased renal permeability or that such a glycosuria is the result of an actual (but masked) hyperglycemia.

DIMINISHED RENAL PERMEABILITY VS. RENAL TOLERANCE FOR SUGAR. A lessened capacity of the kidneys to eliminate sugar, on the other hand, is frequently encountered. The older observers (Naunyn,[8] v. Noorden[9]) as well as the more recent ones (Allen,[10] Macleod,[11] Graham,[12]) make mention of this condition, and numerous instances of persistent hyperglycemia with slight or no glycosuria are recorded. A number of such cases have come under my observation whose blood upon examination yielded the following results:

[6] Epstein, Albert A.: Loc. cit.
[7] Proc. Phys. Soc., London, Jour. Phys., 1916, xlix, 46–48.
[8] Der Diabetes Mellitus, 1906, p. 189.
[9] Handb. d. Path. d. Stoffw., 1907, ii, 7 and 9.
[10] Glycosuria and Diabetes, 1913, p. 48.
[11] Diabetes, its Pathology and Physiology, 1913, p. 48.
[12] Loc. cit.

TABLE VI.

Case.	Blood-sugar, per cent.	Urinary sugar, per cent.
1. G. Web	0.144	0
2. Re	0.195	0
3. Wur.	0.136	0
4. Str.	0.194	0
5. Lei.	0.154	0
6. Adv.	0.162	0
7. Feu.	0.208	0
8. Lev.	0.132	0
9. Gla.	0.324	0.25
10. Bon.	0.260	0
11. De B.	0.216	0
12. Rab.	0.164	0
13. Rub.	0.188	0
14. Mar.	0.324	0
15. Meh.	0.184	0
16. Fruh.	0.172	0
17. Bry.	0.222	0
18. Kay.	0.132	0
19. Sil.	0.190	0
20. Hor.	0.312	0
21. Pin.	0.196	0
22. Elie.	0.280	0
23. Ie.	0.180	0
24. G. Car.	0.264	0
25. Ed. Car.	0.258	0
26. Gin.	0.180	0
27. Sche.	0.200	0

NOTE.—The blood was taken in all the above cases early in the morning, before breakfast, so that the figures represent the blood-sugar content on an empty stomach. The examination of the urine was made on twenty-four-hour specimens, on the same day on which the blood was examined.

The cases presented show varying degrees of hyperglycemia ranging from 0.132 per cent. to 0.324 per cent., without any glycosuria.

It is known that with the approach of coma in diabetes the sugar may disappear from the urine and accumulate in the blood. Clinical and experimental observations of this fact are on record. (v. Noorden,[13] Joslin,[14] Epstein and Felsen,[15] Epstein and Baehr.[16]) Extreme weakness and impaired circulation may also lessen or prevent the excretion of sugar because the kidney function is affected by these conditions.

In febrile states, too, the glycosuria may disappear while the hyperglycemia persists. According to Barrenscheen[17] the diminution or cessation of glycosuria after liberal feeding of oatmeal is due to diminished permeability of the kidneys. The relative infrequency of glycosuria in normal individuals after operative procedures (requiring the use of anesthetics such as nitrous oxide and ether) in whom a definite hyperglycemia develops is attributable to a lessened

[13] Loc. cit., p. 3.
[14] The Treatment of Diabetes, 1916, p. 72.
[15] AM. JOUR. MED. SC., to appear August, 1917.
[16] Jour. Biol. Chem., 1916, xxiv, 1.
[17] Biochem. Ztschr., 1912, xxxix, 232,

permeability of the kidneys.[18]   The use or administration of a number of drugs and chemicals is known to affect the sugar-secreting power of the kidneys, and the development of a chronic nephritis is regarded as a common cause of the cessation of the glycosuria in diabetes.   Thus, many conditions which affect the kidney function may interfere with the glycosuria.

But, whereas, the advent of a chronic nephritis may be associated with the disappearance of sugar from the urine, the latter need not necessarily be the result of the kidney affection.   Very severe grades of renal disease may occasionally be present in diabetes without in any way interfering with sugar elimination.   Two such cases have come under my observation, both dying of undoubted uremia.[19]   In both the nephritis and the diabetes were of long standing; the glycosuria and hyperglycemia however, followed a course common to ordinary uncomplicated cases.   The presence of albumin in the urine of diabetic individuals is very frequent, yet there appears to be no disturbance in the excretion of sugar in consequence of it.

The sugar may disappear from the urine of a diabetic without the intervention of a nephritis.   According to Allen:[20] "The action of the sugar itself is held accountable for the diminished permeability of the diabetic kidney, and it would not be surprising if the kidney should acquire habituation to the long-continued hyperglycemia." A study of the blood-sugar and a close analysis of such cases points to the probability that the cessation of the glycosuria is in many of them the result of an altered state of carbohydrate assimilation rather than the sequel of a diminished renal permeability or sugar "habituation," for, we know that when an active disturbance of carbohydrate metabolism is present, causing a hyperglycemia and glycosuria, any interference with the excretion of sugar by the kidneys results in its accumulation in the blood.   The disappearance of the glycosuria does not mark the cessation of the diabetes.   This is confirmed by the progressive rise in the hyperglycemia.   Clinical examples of this condition are furnished by the cases of Lepine,[21] v. Noorden, Joslin,[22] and also those of the author and Felsen.

Under these conditions the blood-sugar may rise to very unusual heights, 1 per cent. and over, the highest being 1.379 per cent. (Joslin[23]).   Similar results are encountered in experimental animals after pancreatectomy (Epstein and Baehr[24]).

But this is entirely different from the conditions which exist in cases of diabetes, alluded to above (see Table VI), in which the glycosuria vanishes and a hyperglycemia persists without showing any progressive increase.   Liefman and Stern[25] in their researches

[18] Epstein, A. A., Reiss, J., and Branower, J.: Jour. Biol. Chem., 1916, xxvi, 25.
[19] Case L. F.: Incoagulable nitrogen, 0.242 gm. per 100 c.c. serum. Case P. K.: Incoagulable nitrogen, 0.320 gm. per 100 c.c. serum.
[20] Loc. cit.
[21] Rev. de Méd., 1897, xvii, 832.   [22] Loc. cit., p. 72.
[23] Loc. cit., p. 72.   [24] Loc. cit.   [25] Biochem. Ztschr., 1906, i, 299.

on the subject have partly recognized this difference. In order to distinguish between the mechanism which governs the production of a hyperglycemia and that which regulates the glycosuria, they propose the terms "inner" and "outer tolerance" for sugar. The first term applies to the blood-sugar regulation and the ability of the tissues to use it. The second refers only to permeability of the kidneys.[26]

Without some such interpretation the conduct of the blood-sugar in the two types of cases is irreconcilable. Certainly, the term lessened "permeability" of the kidneys for sugar cannot be applied with equal propriety to both. A distinction must be made between the cases in which the disappearance of sugar from the urine results in a progressively increasing hyperglycemia and those in which the cessation of the glycosuria is accompanied by a persistent hyperglycemia which remains fairly constant. There is a clinical difference as well as a pathological one between the two groups: the one indicates failing renal function of a certain type, is rapid in its development, and often signifies the close approach of coma and death; the other is of long duration, often presenting none of the symptoms common to diabetes, and is compatible with good health.

In view of these facts I have applied renal function tests in addition to blood-sugar estimations to a number of cases of diabetes in order to determine the relation of the hyperglycemia and glycosuria to the activity of the kidneys. As stated before, Barrenscheen[27] in studying the influence of oatmeal feeding on the diabetes, found that the resulting decrease in the sugar output was associated with a disturbance in renal function which caused a retention of water and of glucose. Guided by the results of renal tests (lactose and potassium iodide) he came to the conclusion that the oatmeal caused an injury to the glomerulovascular apparatus. His deductions gain support from the fact that the administration of a diuretic, such as theocin, tends to overcome the effect of the oatmeal.

The results obtained in this investigation are therefore of considerable interest and serve to elucidate some of the points under discussion.

Methods. For the determination of renal function, phenolsulphonephthalein was used. Although this substance does not aid in distinguishing different types of renal affections it serves to indicate the presence and extent of functional disorders. An excretion of less than 60 per cent. of the dye in two hours is regarded here as subnormal. The blood-sugar was estimated by means of the microchemical

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[26] In the 2 cases studied by Graham (loc. cit.) the phenomenon (hyperglycemia with little or no glycosuria, or "high—level leak—point" as he terms it) is interpreted as being of the "nature of a protective mechanism." But it is difficult to understand the meaning of "protective mechanism." Does it signify diminished renal permeability or altered carbohydrate utilization?

[27] Barrenscheen, H. K.: Loc. cit.

method of the author,[28] and for quantitative analyses of the glucose in the urine, Rudisch solution was employed.

The observations here recorded were carried out on 60 cases. The blood was obtained for analysis early in the morning on a fasting stomach. Directly thereafter the patients received 6 mgs. of phenol-sulphonephthalein intramuseularly and then were permitted to drink 2 glasses (16 ounces) of water. The patients voided urine at the end of one and two hours. In certain instances the urine was obtained by catheterization. In a number of cases the examination was repeated, for reasons which will be evident later on.

The cases studied may be grouped as follows:

1. Active cases of diabetes untreated:
    (a) Without renal disease.
    (b) With renal disease.
2. Active cases of diabetes rendered sugar-free by treatment:
    (a) Without renal disease.
    (b) With renal disease.
3. Confirmed cases of diabetes which have become sugar-free spontaneously:
    (a) Without renal disease.
    (b) With renal disease (none encountered).
4. Active cases of diabetes showing diminution or disappearance of the glycosuria, but in reality the condition being much aggravated.

TABLE VII.—GROUP I.—UNTREATED CASES OF DIABETES, WITHOUT NEPHRITIS.

Case.	Blood-sugar, per cent.	Urine. 24-hr. specimen, c.c.	Urine. Sugar, per cent.	Phenolsulphone-phthalein. 1st hr., per cent.	Phenolsulphone-phthalein. 2d. hr., per cent.	Excretion, total per cent.
23. M. Le. . .	0.210	3000	2.0	38.0	26.0	64.0
28. Mas.. . .	0.210	2350	4.1	55.0	26.0	76.0
29. Nat. . .	0.300	2250	5.0	48.0	18.0	66.0
30. Ros. . .	0.292	2750	4.1	50.0	15.0	65.0
Average .	0.253		3.8			68.0

UNTREATED CASES OF DIABETES WITH NEPHRITIS.

Case.	Blood-sugar, per cent.	Urine. 24-hr. specimen, c.c.	Urine. Sugar, per cent.	Phenolsulphone-phthalein. 1st hr., per cent.	Phenolsulphone-phthalein. 2d. hr., per cent.	Excretion, total per cent.
9. Gla.. . .	0.324	..	0.25	23.0	28.0	51.0
22. Elie . . .	0.252	..	0.75	13.0	20.0	33.0
10. Bon. . .	0.260	..	0.40	29.0	18.0	47.0
21. Pin. . . .	0.248	1325	1.40	27.0	13.0	40.0
Average .	0.271		0.70			43.0

The figures tabulated above are representative of the results obtained in a large number of diabetic patients upon whom the tests were made prior to the inception of treatment. The table shows that the range of variation of the hyperglycemia in the two types of cases is approximately the same, but the extent of the glycosuria is strikingly different. Comparison is facilitated by averaging the

[28] Epstein, Albert A.: Jour. Am. Med. Assn., 1914, lxiii, 1667.

figures obtained. We thus find that the blood-sugar content in the two groups is 0.258 per cent. and 0.271 per cent.; whereas the concentration of the urinary sugar is 3.71 per cent. and 0.70 per cent., respectively. The phenolsulphonephthalein excretion of these cases seems to parallel the sugar elimination, being considerably lower in the nephritic than in the non-nephritic group, the average for the two groups being 66 per cent., and 43 per cent., respectively.

It would appear from a comparison of the phenolsulphonephthalein excretion and the sugar output of the cases presented that there is a definite relation between the two functions: that disease of the kidneys interferes with the sugar elimination as well as with that of the dye. In view of the approximate equality of the hyperglycemias in the two types of cases and the marked difference in the glycosuria it would seem likely that the kidneys of the nephritic individuals are less permeable to sugar than those of the non-nephritic cases.

However, it does not necessarily follow that the diminished glycosuria observable in the nephritic cases is the result of the renal disease. In the first place, repeated examinations of the blood-sugar in the nephritic cases fails to show any progression of the hyperglycemia, such as that found in cases in which failing kidney function interferes with the elimination of sugar (see Cases 35 and 36); so that the hyperglycemia observed in these nephritic cases is really not the result of sugar retention due to renal "impermeability." Further, withdrawal of carbohydrates from the diet of these individuals leads to a rapid disappearance of the glycosuria, but the hyperglycemia persists. Reference has also been made to the fact that a very severe nephritis may be present and exert no influence whatever on the intensity of the glycosuria nor on the height of the hyperglycemia. For example the two cases of this type previously mentioned presented the following results:

Case A. F. Blood-sugar, 0.300 per cent.; urine, 4440 c.c.; sugar, 5 per cent.; total, 222 grams. Phenolsulphonephthalein, 18 per cent.

A. K. Blood-sugar, 0.218 per cent.; urine, 3600 c.c.; sugar, 4.6 per cent.; total, 165.6 grams.

The quantity of sugar found in the blood at any one moment represents the result of three functions: (1) the rate at which sugar is thrown into the circulation; (2) the rate of its utilization by the tissues; (3) the rate of renal excretion. If the supply of sugar to the blood is in excess of tissue requirement, and more than the kidneys can eliminate, it must accumulate in the blood stream. This has been referred to above and will be demonstrated by specific cases presently. If, therefore, a marked hyperglycemia is present which remains constant over a considerable period of time, causing little or no glycosuria (whether a nephritis is present or not), it signifies that a balance has been established between the rate at

which sugar is supplied to the blood and its utilization by the tissues. This is supported by the findings in a group of cases without renal disease in which the glycosuria disappeared spontaneously or following treatment, but the hyperglycemia remained persistently high. (See Tables VIII and IX.)

TABLE VIII.—GROUP II.—DIABETIC CASES RENDERED SUGAR-FREE BY TREATMENT: NON-NEPHRITIC.

| | | Urine. | | Phenolsulphone- | | |
| | | 24-hr. | | phthalein. | | Excretion, |
Case.	Blood-sugar, per cent.	specimen, c.c.	Sugar, per cent.	1st hr., per cent.	2d. hr., per cent.	total per cent.
25. Ed. Car. .	0.258	1560	0	40.0	22.0	62.0
31. A. Mor. .	0.178	1250	0	44.0	27.0	71.0
17. Bry . . .	0.222	..	0	40.0	22.0	62.0
16. Fruh. . .	0.172	3000	0	57.0	21.0	78.0
14. Mar. . .	0.324	..	0	60.0	15.0	75.0
15. Meh. . .	0.182	..	0	..	..	69.0
24. G. Car. . .	0.264	1600	0	54.0	21.0	75.0
11. De B. . .	0.216	..	0	33.0	23.0	56.0
5. Lei . . .	0.164	2500	0	30.0	29.0	59.0
Average .	0.220					67.0

DIABETIC CASES RENDERED SUGAR-FREE BY TREATMENT: NEPHRITIC.

7. Feu. . .	0.208	..	0	17.0	24.0	41.0
20. Hor. . .	0.312	..	0	26.0	29.0	55.0
32. Trou. . .	0.101	900	0	37.0	9.0	46.0
33. J. Wei. . .	0.213	..	0	28.0	27.0	55.0
Average .	0.217					49.0

TABLE IX.—GROUP III.—CONFIRMED DIABETICS WHO HAVE BECOME SUGAR-FREE SPONTANEOUSLY: NON-NEPHRITIC.

| | | Urine. | | Phenolsulphone- | | |
| | | 24-hr. | | phthalein. | | Excretion, |
Case.	Blood-sugar, per cent.	specimen, c.c.	Sugar, per cent.	1st hr., per cent.	2d. hr., per cent.	total per cent.
19. Sil. . . .	0.196	1500	0	55.0	19.0	74.0
18. Kay. . .	0.132	..	0	40.0	30.0	70.0
6. Adv. . .	0.162	..	0	47.0	17.0	64.0
4. Str. . . .	0.194	2280	0	42.0	18.0	60.0
Average .	0.171					67.0

Among the cases presented in Table VIII there are four with evidences of renal disease. The only difference observable between these latter and the non-nephritic cases is in the amount of phenol-sulphonephthalein excreted. The non-nephritic cases manifest a high blood-sugar content without a glycosuria and the phenol-sulphonephthalein elimination is normal. The group of spontaneously recovered cases is comprised of individuals who were known to have had diabetes but who made no special effort to control the disease. From the stand-point of the glycosuria these cases

might be classed as mild or moderate. However, the blood-sugar in them is high, but not to the same extent as in those which have been rendered sugar-free by treatment. This may be due to a difference in the duration of the sugar-free period. The functional activity of the kidneys in these cases is perfectly normal.

Two deductions appear admissible from these results: (1) that an increased blood-sugar content may be present in diabetic individuals without giving rise to glycosuria even in the absence of renal disease; (2) that the hyperglycemia in the nephritic individuals is no greater than it is in the non-nephritic.

That the hyperglycemia observed in the above cases is not the result merely of a lessened renal permeability, but that of some alteration in the supply and utilization of sugar, is shown by the relative constancy of blood-sugar content which is observed when the examinations are frequently repeated. An illustration of this fact is found in the following cases:

TABLE X.

Case.	Date.	Blood-sugar, per cent.	Urine-sugar.
2. Re.	Jan. 29, 1916	0.195	0
	Nov. 1, 1916	0.220	0
	Nov. 11, 1916	0.180	0
5. Lei.	July 13, 1916	0.154	0
	July 31, 1916	0.148	0
	Aug. 5, 1916	0.162	0
10. Bon.	April 8, 1916	0.260	0
	April 9, 1916	0.244	0
	April 10, 1916	0.250	0
	April 11, 1916	0.260	0
	April 12, 1916	0.210	0
	April 13, 1916	0.200	0
	April 14, 1916	0.220	0
	April 16, 1916	0.240	0
22. Elie.	June 19, 1916	0.280	0
	July 8, 1916	0.320	0
	July 15, 1916	0.320	0

The above cases serve as an illustration of the condition which is encountered in certain cases of diabetes—namely, a persistent hyperglycemia which remains at a constant level. There is no glycosuria, notwithstanding the fact that the kidneys functionate normally in all other respects. From what has been said before we must conclude that a rearrangement of some sort has taken place by which a balance between the supply of sugar to the blood and its utilization by the tissues is constantly maintained. Undoubtedly, the kidneys take part in this process, as other organs do, so that the absence of sugar from the urine does not indicate a lessened permeability (in the sense of inability to eliminate glucose or an active interference with its excretion), nor does it signify "habituation" of the kidneys to the hyperglycemia, for that alone would not be capable of maintaining the blood-sugar content at a constant level.

We must assume, therefore, that the hyperglycemia without a glycosuria which we find in these cases represents a condition in which the supply of sugar is appropriate to the utilization and does not exceed it. The acquired "tolerance" of the kidneys for the hyperglycemia in this sense constitutes a "protective mechanism" (see footnote 26, p. 110) and is different from the mechanism ordinarily understood in the term "lessened permeability."

When the supply of sugar to the blood exceeds the rate of its utilization by the tissues the result is a hyperglycemia. What actually happens when the kidneys fail to excrete the excess is that it accumulates rapidly in the blood and the hyperglycemia mounts progressively. This is illustrated by the cases already referred to (Lepine, v. Noorden, etc.), and the experiments on animals (Epstein and Baehr) mentioned above.

It also has been pointed out that the presence of renal disease and reduced phenolsulphonephthalein excretion may be associated in diabetes, with a marked hyperglycemia and slight glycosuria, and that the latter is not necessarily the result of the nephritis. The question therefore arises concerning the nature of the renal disturbance which is capable of interfering with the glucose elimination, in consequence of which the liberated and unused sugar accumulates in the blood. Reference has been made to Barrenscheen's observations on the effect of oatmeal on the sugar secreting function of the kidneys. The disturbance produced is evidently of a circulatory nature. This is supported by the tests with lactose and potassium iodide instituted by him and by the salutary effect of diuretics upon the disturbance.

The following protocols are therefore of special interest in this connection, because they demonstrate the role of the kidneys in the regulation of the hyperglycemia and glycosuria in diabetes. They indicate, furthermore, that "lessened permeability" is probably identical with failing renal function of a type which may react to therapeutic measures.

GROUP IV.

CASE 35.—A. K.; male; aged sixty-three years; suffering from diabetes mellitus for eighteen years. One week before coming under observation he developed a thrombosis of the femoral artery. Upon examination it was found that the patient had a chronic endocarditis and arteriosclerosis. The urine was small in amount (daily output about 900 c.c.), highly concentrated, and contained a moderate amount of albumin, numerous casts, and some blood cells. The sugar output ranged from 2.0 per cent. to 3.5 per cent. The blood-sugar varied between 0.220 and 0.260 per cent.

Dietary restriction (modified Allen regime) caused a prompt disappearance of the glycosuria. The patient's condition improved and he was gradually allowed more food. Two weeks after the

first observation, when the patient was permitted to sit in a chair, it was noticed that the quantity of urine passed became diminished (660 c.c. per day). It remained sugar-free, but the amount of albumin and formed elements increased. The heart action appeared much weaker, but there was no evidence of cardiac enlargement. The healthy extremity showed slight edema. The blood examined at this time showed a hyperglycemia of 0.412 per cent.

It was evident that the patient at this stage was receiving more carbohydrate than he could tolerate, and because of the circulatory disturbance, which also affected the kidneys, no sugar appeared in the urine. Cardiac stimulation was resorted to (spartein sulphate and infusion of digitalis), with very prompt response in the pateint's condition. The heart action improved; the quantity of urine rose to 1500 c.c. Sugar appeared in the urine (2.2 per cent.) and the blood-sugar dropped to 0.200 per cent.

CASE 36.—A. M.; female, aged forty-two years. Came under observation February 16, 1916, with a history of menorrhagia and diabetes mellitus. Patient stated that when the urine was first examined (some time in January) it contained over 10 per cent. of glucose. The patient complained of the usual symptoms, particularly of the polydipsia and the pruritus vulvæ, both of which were observed one month prior to the date of consultation. Upon examination the patient appeared emaciated, weighing 110 pounds (usual weight 139 pounds). The skin and mucous membranes were dry. Tongue heavily coated; acetone odor to the breath. Heart action rapid (110 beats per minute); sounds fairly good; no murmurs. Pulses small and soft; blood-pressure 112 systolic and 80 mm. diatolic (Merser apparatus). Abdomen lax; liver not enlarged. Marked hyperemia of the vulva; uterus enlarged; tumor mass palpable in the posterior wall.

The patient was put on a restricted diet: 500 grams of 5 per cent. vegetables, black coffee, broths, and small amounts of whisky, 1 to 2 ounces daily. This diet was kept up until the patient became sugar-free, and then gradual additions of other foodstuffs were made.

The clinical course pursued by the patient during the first period of observation (February 16 to March 7), was very favorable. Although there occurred a progressive loss in weight, there seemed to be general improvement. The symptoms originally complained of disappeared and the patient experienced a feeling of well-being. The changes which took place in the blood and urine are recorded in Table XI.

February 17, the first day of observation, the patient eliminated 2000 c.c. of urine, containing 1.2 per cent. of glucose. The blood-sugar was 0.220 per cent., and the phenolsulphonephthalein excretion was 74 per cent. in two hours. March 4 another phenolsulphone-phthalein test was made and the excretion was normal (71 per cent.

in two hours), although the blood-sugar was 0.178 per cent., and the urine was sugar-free. In other words, the hyperglycemia which remained was not associated with any disturbance of renal function.

TABLE XI.—CASE 36.

Date.	Urine.		Ace-tone.	Dia-cetic acid.	Blood-sugar, per cent.	Alveo-lar CO_2.	Phenolsulphone-phthalein excretion.			Remarks.
	Quantity, c.c.	Sugar, per cent.					1st hr.	2d hr.	Total.	
							p. c.	p. c.	p. c.	
Feb. 16, 1916	S.S.	+	+++	+++						
" 17, 1916	2000	1.2	++	++	0.220	..	46	28	74	
" 18, 1916	1500	0.8	++	+						
" 19, 1916	1875	0.6	+	0						
" 20, 1916	1575	0.55	+	++						
" 21, 1916	1950	0	+	0						
" 22, 1916	1600	0	VFT.	0						
" 23, 1916	1375	0	+	0						
" 24, 1916	1250	0	VFT.	0						
" 25, 1916	1200	0	VFT.	0						
" 26, 1916	1600	0	VFT.	0						
" 27, 1916	1200	0	+	0						
" 28, 1916	1400	0	+	0						
" 29, 1916	2150	0	VFT.	0						
Mar. 1, 1916	1600	0	++	0						
" 2, 1916	1125	0	+	0						
" 3, 1916	850	0.7	+	0	0.196					
" 4, 1916	1250	0	+++	0	0.178		44	27	71	
" 5, 1916	750+	0	FT.	0						
" 6, 1916	2725	0	VFT.	0						
" 7, 1916	1200	0.55	+	0	0.182					
June 7, 1916	1200	0.25	+	0	0.284	5.6				
" 8, 1916	1120	0	+	FT.	0.288	5.1				
" 9, 1916	840+	0.43	Tr.	0	0.268	6.0			48	
" 21, 1916	1080	0.2	0	..	0.288	5.1				
" 22, 1916	990	0	0	0	0.324	3.2				
" 25, 1916	1020	0	0	0	0.272					
July 4, 1916	690	0	0	0	0.166	4.2	..	..	34	Edematous.
" 5, 1916	8000	0	0	0	..	..	..	..	..	Inf. digitalis.
" 6, 1916	3500	0	0	0	0.356	..	..	..	..	Edema absent.
" 7, 1916	2400	0.5	+							
" 10, 1916	1980	2.5	++	Tr.						
" 11, 1916	960	2.2	++	+						
" 12, 1916	1320	2.0	++	+						
" 13, 1916	1440	2.0								
" 19, 1916	1500	1.66								
" 21, 1916	1650	1.1	++	0	0.206	3.9			71	

+ = decided reaction.   VFT. = very faint trace.   FT. = faint trace.   Tr. = trace.   Inf. = infusion.   S.S. = single specimen.

In the interval between March 7 and June 7 the patient was seen infrequently and definite observations could not be made. June 7 the patient returned and appeared to be in very poor condition. The urine contained only 0.25 per cent. of glucose, a trace of acetone, and no diacetic acid. The blood-sugar, however, was 0.284 per cent., the highest figure yet attained in this case. On the following day the urine was again sugar-free, but a day later a small quantity of sugar reappeared (0.43 per cent.). The blood-sugar taken then was 0.268 per cent., and the phthalein excretion was only 48 per cent. in two hours, hence much lower than in the previous test. It is evident from this observation that there was a retention of sugar at the time, occasioned by defective function, and consequent decrease in renal permeability.

A slight glycosuria alternating with a sugar-free state continued until June 20. The blood-sugar remained at approximately the same high level. In view of the patient's very low tolerance for carbohydrates (in fact for any food) it appeared advisable to attempt fasting. The result of this procedure was an aggravation of existing conditions. The urine became free from sugar and ketone bodies, but the blood-sugar rose to 0.324 per cent., a still higher level than previously observed. The acidosis also increased, as shown by the alveolar CO_2, which dropped to 3.2 per cent. (Frederici apparatus).

A further rise in the hyperglycemia showed definite progression of the diabetic process, notwithstanding the fact that the urine was sugar-free. The fasting was therefore interrupted. A small quantity of 5 per cent. vegetables was allowed, together with 500 c.c. of milk and two ounces of whisky. Because of the increasing acidosis, bicarbonate of soda (4 grams t. i. d.) was administered. As a result of this treatment the patient's condition seemed to improve. The urine remained free from sugar and acetone and the blood-sugar dropped to 0.272 per cent. It is noteworthy that the daily output of urine in this period has been small, particularly as the thirst and polydipsia were pronounced.

The existing pathological conditions became apparent from the course of events in the next period of observation (July 3 to 21). July 3, contrary to instructions, the patient took a lengthy automobile ride. Before the completion of the trip the patient suddenly became very faint, and upon her return it was found that she seemed swollen all over. A very pronounced general anasarca developed in the next twelve hours. The heart action was slow (48 beats per minute) and feeble. The respirations were slow (12 per minute) and sighing in character. The patient was very drowsy, but responded to questions when aroused.

The urine was sugar-free and did not contain any ketones. The blood-sugar was only 0.166 per cent. The phthalein excretion was 34 per cent. in two hours. The latter, of course, was in keeping with the clinical phenomena, i. e., reduced urinary excretion and the edema, but the relatively low hyperglycemia appeared to be paradoxical. The absence of glycosuria, because of deficient renal permeability, should have caused a retention of sugar in the blood, and hence a greater hyperglycemia. The reason for this discrepancy appears in the developments of the next few days.

Following the therapeutic indications at this stage the bicarbonate of soda was stopped, and the infusion of digitalis, in half-ounce doses, every three hours was administered. The result was most remarkable. In the ensuing twenty-four hours the patient eliminated 8000 c.c. urine, which was free from sugar, acetone, and diacetic acid, and the day following 3500 c.c. of a like urine was passed. The edema disappeared entirely. The blood-sugar examined on the morning of July 6 showed the high figure of 0.356 per cent. The blood-pressure, systolic, rose to 128 mm. The heart

action was more forcible and the pulse-rate 68 per minute. With the improvement in renal secretion, sugar reappeared in the urine, at first 0.5 per cent. (July 7), rising gradually to 2.5 per cent. (July 10). Subsequently it diminished slowly, and on July 21 the glycosuria was only 1.1 per cent. The blood-sugar on that day was only 0.206 per cent. The phthalein test showed again a normal excretion (71 per cent. in two hours).

Thus it appears that during the period of anasarca the lowered hyperglycemia was due to abstraction of sugar from the blood by the edema fluid. With the increased diuresis and the subsidence of the edema the surplus sugar was returned to the blood. Sugar did not appear in the urine until the function of the kidneys improved, and the glycosuria became progressively more intense as renal activity increased. Following the elimination of the retained sugar the hyperglycemia diminished, so that finally when the renal function returned to normal (July 21) we find moderate glycosuria with a corresponding hyperglycemia, comparable to that observed on the day of the first test (February 17).

The above cases (unlike those of Groups 2 and 3, *vide supra*) show that interference on the part of the kidneys with elimination of sugar causes a retention of this substance in the blood, and hence a progressively increasing hyperglycemia. Although we have no conclusive evidence of the exact nature of the renal disturbance which affects the glycosuria and hyperglycemia in this manner, the associated circulatory disturbances make it seem probable that the derangement in the kidneys is of circulatory origin analogous to the condition found after feeding oatmeal (Barrenscheen). The prompt manner in which these cases react to cardiovascular stimulation, with an increase or reappearance of the glycosuria and a fall in the hyperglycemia, makes this deduction all the more likely.

These observations are of importance not only in showing us a phase of kidney function which influences the hyperglycemia and glycosuria, but also because the diminution or cessation of glycosuria in diabetes mellitus, which is accompanied by a progressively increasing hyperglycemia, affects the prognosis and constitutes an important indication for certain therapeutic measures.

We thus encounter two types of cases in diabetes: one in which the disappearance of the glycosuria is associated with a definite retention of sugar in the blood, due to failing kidney function (lessened permeability), which is probably of circulatory origin; the other in which the cessation of the glycosuria is not the result of renal interference. In this latter group the hyperglycemia may persist, but it remains constant—at least it shows no progression. That this is due to a rearrangement of the carbohydrate metabolism, whereby the plane of sugar utilization becomes elevated ("inner tolerance" of Liefman and Stern or "protective mechanism" of Graham), and not due to a lessened renal permeability, is gleaned from the conduct of such cases under special conditions of nutrition,

Since the introduction of the fasting method of treatment of diabetes we have found that the ordinary uncomplicated cases (particularly those of recent origin) show that the disappearance of glycosuria is accompanied by a rapid fall in the blood-sugar, often reaching the normal level. In the group of cases mentioned above (Group 2), fasting reduces the hyperglycemia somewhat, but does not, as a rule, bring it back to normal. In a small proportion of cases considerable reduction in the hyperglycemia may thus be obtained. Macleod mentions one case[29] in which the blood-sugar decreased from 0.183 per cent. to 0.107 per cent., after rigid dietary control. I have found among my cases thirteen instances of reduced hyperglycemia following adequate dietary management, ranging over varying periods of time (see Table XII).

In most instances, however, the hyperglycemia persists long after the disappearance of the glycosuria, notwithstanding fasting and prolonged dietary restrictions.

TABLE XII.

Case.	Date.	Blood-sugar, per cent.	Urine-sugar.
6. Adv.	July 17, 1916	0.162	0
	July 26, 1916	0.066	0
	Aug. 30, 1916	0.098	0
19. Sil.	May 31, 1916	0.196	0
	June 19, 1916	0.115	0
	July 3, 1916	0.080	0
4. Str.	July 16, 1916	0.194	0
	July 30, 1916	0.094	0
	Sept. 8, 1916	0.116	0
	Sept. 21, 1916	0.105	0
32. Trou.	Oct. 28, 1915	0.164	0
	Aug. 24, 1916	0.101	0
25. Ed. Ca.	Jan. 3, 1916	0.300	0
	Nov. 7, 1916	0.194	0
	April 17, 1916	0.258	0
	Aug. 23, 1916	0.162	0
15. Mch.	June 6, 1916	0.182	0
	Aug. 15, 1916	0.100	0
7. Feu.	June 19, 1916	0.208	0
	Aug. 30, 1916	0.112	0
	Sept. 25, 1916	0.110	0
16. Fruh.	July 17, 1916	0.172	0
	Aug. 16, 1916	0.136	0
5. Lei.	July 10, 1916	0.164	0
	Sept. 2, 1916	0.142	0
	Sept. 8, 1916	0.104	0
	Sept. 28, 1916	0.103	0
27. Sche.	Nov. 6, 1914	0.200	0
	May 15, 1916	0.075	0
2. Re.	Jan. 15, 1916	0.260	0
	Jan. 29, 1916	0.195	0
	Nov. 11, 1916	0.180	0
21. Pin.	April 1, 1916	0.248	0
	April 8, 1916	0.196	0
34. Toc.	Sept. 19, 1915	0.190	0
	Sept. 16, 1916	0.109	0

[29] Macleod, J. J. R.: Loc. cit.

SUMMARY AND CONCLUSIONS. 1. A condition simulating renal diabetes, *i. e.*, a glycosuria without hyperglycemia, may occur in diabetes mellitus. This is brought about by an increase in blood volume which reduces the concentration of the blood-sugar, and the consequent fall in its percentage masks the hyperglycemia. In order, therefore, to prove the existence of a true renal diabetes it is necessary to show that the total sugar content of the blood is not increased above normal.

2. Hyperglycemia without glycosuria is of frequent occurrence in diabetes mellitus. When sugar is absent from the urine a persistent hyperglycemia which remains constant or does not show progression indicates an altered state of carbohydrate metabolism in which a balance is established between the supply of sugar to the blood and its utilization by the tissues on a higher plane than that found normally. This is interpreted as a condition of increased "tolerance" of the kidneys for sugar and not that of "lessened permeability."

3. Renal disease (true nephritis) need not interfere with the elimination of sugar. The cessation of the glycosuria in diabetes mellitus when a nephritis supervenes is not necessarily the result of the kidney affection. Increased tolerance of the kidney for sugar may exist when a nephritis develops. The two conditions may be synchronous or coincident.

4. Lessened permeability of the kidneys, *i. e.*, interference with the excretion of sugar in the course of an active diabetes, leads to the progressive accumulation of sugar in the blood. The glycosuria may diminish or disappear entirely. This clinical complex portends the approach of coma and appears to be due to a circulatory disturbance of the kidneys associated with a general cardiovascular asthenia. The administration of appropriate medication may overcome the disorder. Improvement manifests itself by reappearance of the glycosuria, with a consequent fall in the hyperglycemia. The development of an anasarca may cause a fall in the percentile blood-sugar content and thus conceal the retention of sugar. This is due to the abstraction of sugar from the blood by the edema fluid. The subsidence of the anasarca causes a return of the hyperglycemia.

5. Testing the kidney function by means of phenolsulphonephthalein in diabetes mellitus is a useful procedure. It aids in understanding the relation of the hyperglycemia to glycosuria. It is particularly helpful in those cases in which a fall in the urinary sugar is associated with a rise in the blood-sugar, thus yielding confirmatory evidence of the fact that the elimination of glucose is interfered with.

REVIEWS

FRACTURES AND DISLOCATIONS. By L. A. STIMSON, B.A., M.D., LL.D. Yale; Professor of Surgery in Cornell University Medical School, New York; Consulting surgeon to New York and Bellevue Hospitals, etc. Eighth edition. Pp. 946; 475 illustrations and 39 plates. New York and Philadelphia: Lea & Febiger, 1917.

THE fact that this is the eighth edition of the excellent work is insurance enough of the value of its text and the appreciation of its work by the profession at large.

The principal changes and additions in the work are in the line of treatment. In recent years there has been marked increase in the interest taken in fracture treatment. The great number of fractures treated among the soldiers has also added much to the available knowledge of the more obscure points. The author in two visits to France saw a great deal of the fracture work done by many of the ablest surgeons in the world and has consequently enhanced the value of his work by such additions.

The book describes in detail many of the newer forms of suspension and extension treatment of fractures both simple and compound. Illustrations of such dressings are included and add greatly to the value of the text in that they show us the important details accurately. Throughout the work, the treatment is given great consideration and no minutiæ is too unimportant to describe. This is a very good principle, for so many books on fractures neglect this very vital point. Furthermore, great stress is justly and wisely laid upon traction and extension as a very important feature in certain types of injury.

In the chapters on dislocations, the largest addition has been on the subject of the dislocations of the shoulder in infancy—birth dislocations and the posterior subluxations. A short section on subluxation of the great horn of the hyoid has also been added.

The work is an exceedingly valuable one by virtue of its completeness, lucidity of detail and great number of good descriptive illustrations.   E. L. E.

SURGICAL OPERATIONS. By KRAUSE, HEYMAN and EHRENFRIED.
Vol. II. Pp. 715; 373 illustrations. New York: Rebman
Company, 1917.

THIS volume, the second of a series of six, deals with the surgical
operations on the jaws, the mouth, pharynx, salivary glands, facial
and cervical nerves, and brain. It is written in German primarily
and translated into English by Albert Ehrenfried. The book is
larger than need be, due to wasted space in wide margins and
unnecessarily large illustrations. Although the authors designate
the work as one of surgical operations, they consume lots of valuable
space with daily clinical notes on their operative cases in many
instances. They also devote too great description of network of
veins, small arteries, etc., that they mention but only to suggest
their probable identity. These digressions are very helpful and
exceedingly interesting from the clinical standpoint, but tend to
make an operative surgery too cumbersome.

With these exceptions the work is a very good one. The text is
clearly pleasing, presented despite a definite inclination toward the
foreign style of expression. The plates are excellently executed in
color and are very descriptive of the point they intend to depict.

The volume is really much more than are operative surgery. In
addition to describing the operations in more or less detail, it takes
up the clinical phase and also refers repeatedly to other author's
works.

Many of the operations described are but seldom seen so that the
book really brings us something almost entirely new in many
respects.   E. L. E.

A TEXT-BOOK OF HISTOLOGY. By FREDERICK R. BAILEY, A.M.,
M.D. Fifth edition. Pp. 652; 392 illustrations. New York:
William Wood & Co.

THE present edition shows but slight changes from the previous
one, reviewed in this JOURNAL, 1915, vol. cl., p. 130. The demand
for a new printing shows that the book has attained a place among
standard tests for the instruction of students in normal histology.
The chapter on the central nervous system by Dr. O. S. Strong,
containing a little over 100 pages, is quite comprehensive. It gives
not only the histology of important regions, but also descriptions
and illustrations of cross-sections of the brain stem at various levels,
and diagrammatic charts to show the course of the more important
pathways. To anyone desiring a succinct and well-balanced account
of the internal structure of the nervous system, a study of this
presentation of the subject will be interesting.   W. H. F. A.

THE PATHOLOGY OF NEPHRITIS. By WILLIAM OPHÜLS, Division of Pathology. Stanford University Medical School. Pp. 103; 64 photographs and photomicrographs. Published by the Stanford University, California.

THIS small book consists of a record of thirty-two cases of acute, subacute and chronic glomerulonephritis. Of each case a brief clinical history, the urinary findings, the blood-pressure, eye-ground findings and in some case phthalein tests are given. A detailed description of the gross and histologic pathology of the kidney follows the clinical record and a microphotograph of the kidney of each case is included. The author discusses the cases in four groups: acute, early subacute, late subacute and chronic cases, and draws certain conclusions from the series.

As a collection of carefully studied cases the book is of much interest to the investigator in renal pathology and might serve a useful purpose in furnishing the student with a larger series of cases of these types of nephritis than he would be likely otherwise to have presented to him. J. H. A.

BONE AND JOINT STUDIES. By LEONARD W. ELY, Associate Professor of Surgery (Orthopedics), and JOHN FRANCIS COWAN, Assistant Professor of Surgery in Stanford University. Pp. 139; 41 illustrations: Stanford University Publications.

THIS pamphlet presents the results of experimental work by the authors on dogs and rabbits in connection with the following subjects: Experimental resection of the dog's knee-joint; reaction of the tissues of the knee-joint of the rabbit to injury; a study of one hundred dry bones sawed in the laboratory; a study of the sterno-clavicular joint. A summary of each experiment is given and conclusions are presented at the termination of each piece of work. T. T. T.

PRINCIPLES OF TREATMENT OF BROKEN LIMBS. By WILLIAM F. FLUHRER, Consulting Surgeon to Bellevue and Mount Sinai Hospitals. Pp. 122; 31 illustrations. New York: Rebman Company.

BEGINNING in 1872, while a member of the House Staff of the Bellevue Hospital of New York, the author devised a method for the more speedy fixation of the fragments of a fracture in adjusted relations. This was accomplished by means of the use of roughened narrow tin strips and plaster-of-Paris bandages for the construction of the permanent retentive apparel. Special emphasis is given to

the author's apparatus for the setting and fixation of the fragments of a fracture of the femur. Its inexpensiveness, ease of construction and apparent effectiveness, call for special consideration now in view of the great difficulties to be met with in the treatment of such fractures under war conditions. Open operation in simple fractures, septic wound complications, compound fractures and primary amputations, receive especial attention   T. T. T.

A PRACTICAL MEDICAL DICTIONARY. By THOMAS LATHROP STEDMAN, A.M., M.D. Fourth revised edition. Pp. 1102; illustrated. New York: William Wood & Co.

THE reviewer had the opportunity of reviewing a previous edition of this work, the second; at that time the dictionary, from a rather hasty perusal of its contents, was spoken of in extremely commendatory terms. Since then this second edition has been in constant use. During the past four years but three words were found in the literature which upon referring to the book were not incorporated in it. In the present edition, the fourth, the reviewer finds not only these three words but also more than two thousand others!—a splendid commentary of the additions that have been made. After all the *sine qua non* of a dictionary is the number of definitions, and in the present volume the writer has been unable to find any words omitted. As to the correctness of the spelling, the character of the definitions themselves, and the pronunciation of the words, the name of the scholarly and erudite author assures us of their authority.   J. H. M., JR.

A TEXT-BOOK OF PATHOLOGY. By ALFRED STENGEL, M.D., Sc.D., Professor of Medicine, University of Pennsylvania; Physician to the Pennsylvania and to the University Hospitals, and HERBERT FOX, M.D., Director of the Pepper Laboratory of Clinical Medicine, University of Pennsylvania; Pathologist to the Philadelphia Zoölogical Garden. Sixth edition. Pp. 1045; 468 illustrations, with 15 colored plates. Philadelphia and London: W. B. Saunders Company.

DR. STENGEL's *Text-book on Pathology* was thoroughly and carefully revised in 1915 in coöperation with Dr. Herbert Fox. The present volume is a resetting of this sixth edition. In some ways this edition is comparable to the earlier previous ones, which have made the book a standard among pathological text-books. In many ways, however, extensive changes have been made, first in order to incorporate more of the pathological physiology, the study of

which has become so important to modern every-day medicine, and second to enlarge and extend the consideration of pathogenesis of diseases. In spite of these additions it would seem to the reviewer that even greater additions to these two sections would be of value. Pathology nowadays is concerned not only with the gross and microscopic changes that occur in the organs as a result of disease, but also takes into consideration the changes that occur as a result of the disturbance of functions that occur as a result of pathological changes. The value of the book would be greatly enhanced if such alterations in the physiology of pathological organs were enlarged and dealt with more extensively.   J. H. M., JR.

DISEASES OF THE STOMACH, INTESTINES AND PANCREAS. By ROBERT COLEMAN KEMP, M.D., Professor of Gastro-intestinal Diseases at the Fordham University Medical School; Gastro-enterologist at the Fordham University Clinic. Third edition, revised. Pp. 1096; 438 illustrations. Philadelphia and London: W. B. Saunders Company, 1917.

THE third edition of this standard work appears enlarged and greatly improved in form. The book is extremely well written and absolutely complete in every way, and is one which the general practitioner may depend upon for a complete knowledge of a subject which is daily brought to him. The additions of this third edition include most notably a complete expedition of the roentgen ray as an aid to diagnosing particularly the organic defections of the stomach and intestines. Dr. Kemp has also incorporated the newer ideas in regard to protein infection, diverticulitis, and so on. It is a pleasure to commend the book.   J. H. M., JR.

DIAGNOSIS AND TREATMENT OF ABNORMALITIES OF MYOCARDIAL FUNCTION. By T. STUART HART, A.M., M.D., Assistant Professor of Clinical Medicine in the College of Physicians and Surgeons, Columbia University. Pp. 320; 248 illustrations.

A GROWING importance of cardiac arrhythmias and the necessity of recognizing them when they appear is important. A book such as the present one written by Dr. Hart not only is of scientific importance, but a great clinical necessity. The various irregularities are considered fully and due prominence is given to those which are the most important. The book is to be thoroughly recommended and will prove extremely valuable to those who are interested and sufficiently scientific to wish to study carefully the various phases of cardiac pathology in its broader scope.

                                                J. H. M., JR.

A Treatise on Diseases of the Skin. By Henry W. Stelwagon, M.D., Ph.D., Professor of Dermatology, Jefferson Medical College, Philadelphia. Eighth edition, thoroughly revised. Pp. 1309; 356 text illustrations and 33 full-page colored and half-tone plates. Philadelphia and London: W. B. Saunders Company.

It is always a pleasure to review a volume which has the uniform excellence of Dr. Stelwagon's treatise. In reviewing the last five editions, in each, the author has accomplished his purpose of bringing the volume absolutely up to date. There is no cutaneous treatise that is more replete with reference, thereby giving the investigator, even if not a dermatologist, the opportunity for further study. The same high class of photographic art is exhibited, as in past editions; the new illustrations are uniformly good. The following diseases have either been added to the present volume or the sections dealing with the same revised: Occupational dermatose; paraffinonia; purpura annularis telangiectodes; xanthoma elasticum; ulerythema ophryogenes; pellagra; angioma serpiginosum; erythema elevatum diutinum; pemphigus neonatorum (impetigo contagiosa bullosa neonatorum), leprosy; the leukemias; eczematoid ringworm, and others.

Although there are many books published, a few of which excel the present volume in some detail or other, particularly the pathological aspect, there is none, however, all phases of the treatise considered, that surpasses the same.   F. C. K.

Fats and Fatty Degeneration. By Martin H. Fischer, M.D., Eichberg Professor of Physiology in the University of Cincinnati, and Martin O. Hooker, M.D., Instructor in Physiology in the University of Cincinnati. Pp. 155; 65 illustrations. New York: John Wiley & Sons, Inc., 1917.

The book, or really monograph, is a collection and amplification of the results of experiments which have not ever before been published in English except in abstract form in Science. In the preface the authors say: "While our earlier colloid-chemical studies has compelled a desultory consideration of some of the problems here dealt with, this detailed study of the question of the fat in the cells is less than two years old. We turned to this fat problem in order to escape from older colloid-chemical studies on edema nephritis and allied subjects. Without intent on our part the conclusions of these newer studies dovetail with and corroborate the older ones. A house previously looked at from within is here seen from without—but it is the same house."

The novel scheme of giving an abstract of the entire monograph

in the first chapter is followed so that the busy man may get the gist of the subject matter. In this chapter, which is divided into ten parts to correspond with the ten chapters of the book, reference is made to specific pages in the book proper, so that elaboration on any particular point may be obtained with the least trouble.

The work should prove of interest alike to the chemist, biologist, and physician.   H. E. D.

THE PHYSIOLOGY OF THE AMINO-ACIDS. By FRANK P. UNDERHILL, Ph.D., Professor of Pathological Chemistry, Yale University. Pp. 169; photograph and 12 charts. New Haven: Yale University Press, 1915.

IN preparing this book the author's aim has been "to gather together in one place the results which have thus far been obtained in the field of the biochemistry of the amino-acids, thus affording the busy practitioner, and others whose resources for consulting original communications are limited, an opportunity to gaining a knowledge of the present-day problems in this field of nutrition." For those who wish further information, references are given at the end of each chapter. An adequate knowledge of the fundamental principles of metabolism is presupposed as a preliminary to the proper understanding of the subject matter presented.

The derivation of amino-acids from proteins, the digestion, absorption, and excretion of the amino-acids, the theories of protein metabolism, the fate of the amino-acids and their relation to the specific dynamic action of proteins, the role of the amino-acids in nutrition and growth—all are dealt with briefly but concisely. The physician may complain that the book does not bear enough toward the clinical side, but it should be remembered that the attempt has been rather to indicate leading lines of thought to enable one to keep abreast of the times. It is to be hoped that the books of this form will continue to be written, so that the important findings of any one subject may be immediately available.

The book contains some misprints, the most glaring one being the formula for dextrose, which is given as $C_6H_6O_6$ twice on page 111 and twice on the following page.   H. E. D.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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d-Glucose Tolerance in Health and Disease.—WILDER and SANSUM (*Arch. Int. Med.*, 1917, xix, 311) publish the results of investigations upon the tolerance of healthy and diseased individuals for glucose administered intravenously and at a constant rate. They used for the injection of the glucose solutions the apparatus described by Woodyatt and themselves (*Jour. Am. Med. Assn.*, 1915, lxv, 2067) which consists of a small pump driven by an electric motor, and so arranged that both the stroke of the pump and the number of strokes per minute may be increased or decreased at will. This permits of easy regulation of the rate of injection. They discuss the older methods of determining the sugar tolerance of animals, such as feeding experiments, subcutaneous injections, etc., and show that to accurately estimate tolerance, all factors which influence the rate at which the sugar enters the blood stream must be known. This is manifestly impossible to do when sugar is fed and absorbed through the alimentary tract, or when it is injected subcutaneously and absorbed from that locality. Therefore, if it is put directly into the blood stream at measured and carefully controlled rates, these errors immediately disappear. In order to have all conditions similar in the various experiments, the subjects for the tests were placed on a general mixed diet for several days preceding, none being given excessive amounts of carbohydrates. Only patients between twenty and forty-five years of age were used (one child of fourteen years), and the subjects remained at rest in bed on the day of the experiment, the injections being made between 2 and 4 P.M. No food was given by mouth on the day of the test, and in order that there should be no possible delay in glucose excretion once

the tolerance limit was passed, water was given by mouth during the day in such amounts that the subject received during each hour of the fore-period a quantity similar to that which he would receive during each hour of the test. A preparation of d-glucose of Merck was used at first, and later a high grade commercial glucose purified in the laboratory by decolorization with animal charcoal and repeated crystallization from alcohol. An 18 per cent. solution was finally fixed upon as the most satisfactory concentration for these experiments. The solutions were made with freshly distilled water, and in no test did the subject suffer any chill, shock or other general reaction. In 2 cases thrombosis of the vein used for the injection resulted, but in neither case was there any permanent ill effects. The injections are begun at a rate less than the estimated limit of tolerance and continued long enough to permit of thorough saturation of the tissues before the urine is collected and tested for sugar. This requires about twenty or thirty minutes. If the limit of tolerance has not been reached, the rate is increased, and in thirty minutes another specimen of urine is collected and tested for glucose. Two healthy men and two healthy women were used as the subjects in which to determine the normal limit of tolerance. This was found to be between 0.8 gm. and 0.9 gm. per kilo per hour. Three cases of pancreatic disease were tested and showed tolerance of 0.7 gm. per kilo per hour, 0.5 gm. per kilo per hour and 0.4 gm. per kilo per hour, respectively. Five patients with exophthalmic goitre were examined (2 men and 3 women), and in each case the tolerance limit for glucose was lowered; 2 severe cases showed a tolerance below 0.5 gm. per kilo per hour; two milder cases below 0.6 gm. per kilo per hour; and a still milder case had a tolerance limit between 0.6 and 0.7 gm. per kilo per hour. These findings are in harmony with the decreased tolerance shown by alimentary glycosuria in exophthalmic goitre patients observed by Kraus and Ludwig and others. A typical case of myxedema showed a normal tolerance, which is at variance with the results obtained in feeding experiments, in which an increased tolerance is found. A delay in the absorption rate is possibly the explanation of these results. Two cases of acromegaly, 1 case of suspected gigantism, and 2 cases of dyspituitarism showing Frölich's syndrome were tested, and all were found to have essentially normal tolerance limits. Here, again, the findings differ from those obtained on oral administration, and suggest that, as in myxedema, the increased alimentary tolerance must result from a delay in the rate of absorption from the bowel. One case of alcoholic cirrhosis gave a normal tolerance limit. The authors conclude that this method of determining the tolerance of patients for d-glucose is a practical clinical procedure, and is more accurate and gives more constant results than any other method which has been devised.

Septicemia due to Micrococcus Tetragenus.—Micrococcus tetragenus has largely been ignored as a pathogenic organism for man, but among the many other new medical facts which the war in Europe is eliciting are some interesting observations upon its pathogenicity which are reported by A. H. BIRKS, R. H. THORNBY and R. A. FAWCUS (*Quart. Jour. Med.*, 1916, x, 1, 37–38). The authors state that a large group of cases coming to the hospitals at the front in France are cases

which are clinically indistinguishable from paratyphoid fever, and in which none of the organisms of the typhoid group can be demonstrated. Professor Jacques Carles mentions three varieties of blood infection which produce these illnesses: (1) Micrococcus tetragenus, (2) pneumococcus, (3) Bacillus coli. The tetragenus infection is probably the most frequent, followed closely by the pneumococcal infections. These cases of obscure fever fall into two groups: The first resembles paratyphoid fever, and the second, in which the fever is intermittent, is called "trench fever." The authors believe that certain of the cases of these groups are infectious with Micrococcus tetragenus, and while not able to exclude absolutely this organism as a secondary invader following a primary paratyphoid, they believe this view to be highly improbable. In blood cultures from 100 consecutive cases of obscure pyrexia they isolated Micrococcus tetragenus in pure culture on twenty-five occasions, the cases of tetragenus infections possessing some rather characteristic features. It is apparently the weaker individuals who are most susceptible to the infection, and there seems to be some evidence that it is mildly infectious, as hospital orderlies are liable to contract it. The onset is usually sudden, though occasionally insidious, and the patient has headache, pain in the lumbar region and in the legs from the knees to the ankles. Tenderness over the tibiæ is common, and rather frequently an enlarged spleen and rose spots may appear. Anemia is common, and the patients are characteristically lethargic. The fever is of long duration (ten days or more in their reported cases), sometimes continued and sometimes remittent in character. The patients' serum agglutinates Micrococcus tetragenus, showing that the body has reacted to this organism. The authors had no fatal cases, so that no autopsy material was available, but they conclude that because of its frequency and its long duration it is of great military importance.

Results of Treatment of Hodgkin's Disease.—The generally accepted hopelessness of Hodgkin's disease, and its wholly unsatisfactory treatment are questioned by YATES and BUNTING (*Jour. Am. Med. Assn.*, 1917, lxviii, No. 10, 747). These authors discuss briefly the principles of treatment largely developed by them, and present the results of these methods applied in the treatment of 63 cases of the disease embracing all of its stages. They contend that treatment of the disease must be based upon the assumption that the pathological process involved partakes of the characters of a malign infection and of neoplastic growth, and they divide the cases into two groups, the first group consisting of the acute cases in which the disease runs its course to a fatal termination in a few months, and the second comprising the more chronic cases in which the end is reached in from two to five years. They also provide a scheme of classification for the chronic cases. The first principle which must be recognized in treating Hodgkin's disease is that, in the course of the illness, there are repeated and almost successful arrests of the morbid process, so that conclusions as to cures must be made only after a lapse of five years, during which time the patient has shown no evidence of the disease other than possibly a permanently subnormal lymphocyte count. The active treatment consists first in the e'imination of possible portals of

entry for the infection (assuming that infection plays a part), such as inflamed tonsils, infected teeth and accessory sinuses, etc., followed by the radical extirpation of all involved lymphoid tissue that can be reached, that this infected tissue may not be a drain upon the patient's resources and further source of infection. This surgical interven-tion should be followed by thorough use of the roentgen ray, just as in removals of carcinomatous tissue. Immune sera, medication and general hygienic measures are also used to prevent extension of the disease. The authors state that wide surgical removal of the infected tissues, preceded by careful elimination of all possible portals of entry, and succeeded by careful and thorough use of the roentgen ray, can be successfully done with not more than 5 per cent. of local recurrences, or dissemination of the disease. They insist that the removal of tissue should be as complete as possible, and advise against "test excisions" except as a last resort in doubtful cases, where a frozen section diagnosis will be immediately followed by wide extirpation, or where the positive diagnosis will balance any danger to the patient which may result from possible dissemination of the disease. These excisions should be followed by the use of the roentgen ray. While not able to prove an etiological relationship of B. Hodgkini to the disease, the authors strongly advocate the use of an immune serum prepared with this organism because they have seen local reactions follow its use, with resulting diminution in the size of the glands, reduction in temperature and improvement of the subjective symptoms. Also they believe that patients who receive the serum and the general treatment do better than those who undergo the same general treat-ment without the serum. Arsenic they find to be of no lasting value, and they depend upon fresh air, sunshine and proper food, omitting all drugs other than tonics, which may be used if there is need for them. The results of these methods of treatment vary in the different groups of cases. The acute cases in the authors' words "are about as amenable to treat as is the mastitis carcinomatosa of lactation or melanoma." The incipient chronic cases in which only a few glands adjacent to an infected tonsil or other portal of entry are involved are exceedingly amenable to treatment consisting of the removal of the portal of entrance, roentgenotherapy and general hygienic measures. The diagnosis of these early cases is only made by careful physical examina-tions, routine blood counts and accurate interpretation of tuberculin tests. The authors estimate the possibility of recovery of the various groups of cases as follows: 5 acute cases, less than 5 per cent.; 5 incipient cases, 80 to 90 per cent.; 3 early cases, 60 to 70 per cent.; 11 moderately advanced cases, 30 to 40 per cent.; 14 advanced cases, 5 to 10 per cent.; 14 very late cases, palliation possible, 0 per cent.; 11 lethally involved cases, 0 per cent. The authors regret that as 67 per cent. of their patients presented themselves within the last two years they are unable to give more accurate figures as to ultimate recoveries. They believe that in 20 per cent. of all cases as seen by them recovery is possible, and they urge the importance of early diagnosis and the recognition of the fact that prompt and radical treatment may result in permanent recovery from Hodgkin's disease.

SURGERY

UNDER THE CHARGE OF

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The Principles of the Transfusion of Blood.—STANSFIELD (*Lancet*, i, 489) says that transfusion has been successfully employed in the treatment of various kinds of anemia and in the arrest of spontaneous hemorrhage. It has also yielded promising results in cases of serious infection and in certain toxemias. The ultimate prognosis in cases of anemia depends upon the power of reaction in the bone marrow, and this can only be adequately determined by observing the results of treatment. In cases of pernicious anemia both increased red-cell production and diminished red-cell destruction may result from the transfusion. The age of the patient, duration of the disease, and condition of the bone marrow as indicated in the peripheral blood have hitherto proved the best guides to the progress subsequent to the transfusion. The optimum dosage for transfusion is not yet determined, but it is probable that moderate repeated doses are preferable to large single doses in the treatment of chronic anemis. Very small doses may sometimes be of value. The donor should be a healthy adult with negative Wassermann reaction. The serum of the donor should not agglutinate the corpuscles of the patient, and the serum of the patient should not agglutinate the corpuscles of the donor. Agglutinins should be excluded by tests done immediately before the transfusion, and a single examination is not sufficient to establish the compatibility of the two bloods on all future occasions. If agglutinins are absent, hemolysins will also be absent. If there be great urgency and testing of the blood of the patient and donor be impracticable a small preliminary transfusion should be done half an hour before the main mass of blood is transfused, so that gross incompatibility may be recognized in time. Febrile reactions occur after about 25 per cent. of transfusions even though the bloods of donor and patient have been proved to be "compatible." Rigors occur in about 10 per cent. of the cases. It may prove desirable to investigate the blood of donor and patient with regard to factors of which we as yet know nothing, not merely for the sake of avoiding accidents, but also to determine whether a given donor is likely to afford the maximum of benefit in a particular case. The indirect method of transfusion, employing a glass received and sufficient sodium citrate to prevent coagulation of the transfused blood, is simple and involves no special dangers.

The Surgery of Amputation Stumps, Based on the Experience of 2000 Consecutive Cases.—HUGGINS (*Lancet*, 1917, i, 646) says that the surgery of amputations has entered a new era with the war. The old surgeons planned their operations essentially for speed and for the use

of peg limbs, and the classical operation for the foot belonged to an age when artificial joints had not been introduced. Primary amputations are performed to arrest infection and so to save life. Further operation, or radical treatment, is commonly necessary in England to prepare or improve, so that eventually a satisfactory limb may be fitted to it. The aim of this article is to elucidate this secondary treatment—that is, the preparation of stumps for artificial limbs. It is concluded that: No secondary amputations should be performed in cases of guillotine amputations until all edema has disappeared and skin extension has been employed for six weeks. Guillotine amputation stumps above the middle of the leg or thigh should never be shortened until healed unless it is decided that the knee-joint or hip must be sacrificed. When shortening has to be done the minimum amount of bone necessary for utilizing the joint above should always be borne in mind. A guillotine amputation may make a satisfactory stump in the leg and thigh, and almost always does in the forearm and arm without further re-amputation. Bone in a stump does not necrose unless infected. Delay in shortening stumps reduces the risk of infection, because infection is not in the wound only but in lymphatics leading from the wound. The amount of matting round the vessels leading to or from an amputation stump is very striking. Silk should never be used in operations on stumps. Amputations should be done by skin-flaps only, and no muscle should be used in the flap, the pad of fibrous tissue formed over the end of the bone from the organizing clot being all that is necessary. All nerves, and not merely the main nerves, must be shortened at the time of the amputation or reamputation. To prevent deformity, daily exercising the joints and the employment of splints and bandages are essential measures in preparing the stump for the artificial limb. A good Syme amputation leaves the patient with little disability, and amputations through the tarsus should never be done as a secondary amputation.

Results of Local Anesthesia in Prostatectomy.—LEGEU (*Jour. d'Urolog.*, 1914–1915, vi (published in March, 1917), 601) reports his results with local anesthesia in 150 prostatectomies. He does the suprapubic operation and gives 0.01 centigram of morphin preliminary to the operation. He injects into the bladder 40 to 50 c.c. of the anesthetic solution, which is a 1 to 200 novocain solution to which a small quantity of adrenalin is added. No further anesthetization of the bladder wall is employed. When the bladder is opened two fingers of the left hand are introduced, facing the pubis, and they guide the special needles, long and bent into different angles. With these a series of injections of 5 or 6 c.c. of the solution are made around the adenoma, between the prostate and rectum, and anterior to the urethra. The eneucleation is then begun and is completed in about fifteen minutes. It has not been found necessary in any of his cases to give a general anesthetic. From 250 to 300 grams of the solution are employed, including the 40 grams injected into the bladder.

Scoliosis (Treatment).—ABBOTT (*Am. Jour. Orthop. Surg.*, 1917, xv, 244) summarizes the effective treatment of mild cases of scoliosis as follows: The posture of the deformity must be known. The normal physiological position from which it develops must be recognized, and

the principles of treatment—overcorrection and fixation—must be applied. The overcorrection consists of forcing the spine by the use of a corset into the normal scoliotic posture diametrically opposed to the deformity. The corset must be made from a plaster-of-Paris model, with the overcorrection position exaggerated. The corset must exert pressure at those points only when force is needed to bend the spine into the overcorrected position. The corset will do more harm than good unless accurately adjusted. The corset must be made with sufficient room for the patient to move over into the overcorrected position after treatment has been in operation for a time unless this is accomplished at once. The efficiency of the corset is to be determined only by taking skiagrams through it and by noting the position of the spine. Fixation in overcorrection must be continued until the structures are so changed that they are symmetrical. Unless a perfect balance or equilibrium of the spine is obtained the deformity is not completely reduced. In many cases the corset treatment must be supplemented by exercise, both active and passive, in order to obtain overcorrection. The exercise are given within the corset and with it removed. Exercises are given only in the direction of overcorrection, or in a direction that will not cause the body to assume the deformed position. After fixation has been maintained long enough to cause the necessary changes in the structures the overcorrection corset must be discarded. A straight corset may be of benefit for a time after the overcorrection corset has been discarded, in order to accustom the patient to the straight position. The after-treatment is important, and exercises which are symmetrical, together with massage, are indicated. The deformity must be attacked in the same manner as club-foot, and the same sound surgical principles of treatment that are so effective in reducing that deformity, must be applied, namely, overcorrection and fixation.

Pernicious Anemia, with Special Reference to Its Surgical Management.—PERCY (*Surg., Gynec. and Obst.*, 1917, xxiv, 533) says that we do not know why a given case will fare better without than with the spleen. Up to the present time no constant and typical pathology in the spleen has been observed. The changes found are such as could have been caused by an infective process, the effects of which are evidenced by fibrosis throughout and a moderate increase of lymphocytes. Phagocytosis of degenerated red cells is much more pronounced. The pulp areas are at times greatly crowded and dilated by red cells in various stages of degeneration. It would seem then that there is some process going on in the spleen which causes an increased destruction of red cells. While there can be very little doubt as to the theory of pernicious anemia being a hemolytic disease, it is not certain as to where or in what manner the hyperhemolysis takes place. A splenectomy, even in some of the late cases of pernicious anemia, has been followed by cessation of the hyperhemolysis, indicating that the spleen is at least an important link in the chain necessary for the production of the disease. While no surgeon can say that a cure has resulted from splenectomy or other surgical procedures in any case of pernicious anemia, still there is enough clinical evidence to show that the benefits derived from surgery are more than by any other means. Surgical treatment means more than merely splenectomy. The routine emphasized by Percy is:

Multiple, massive transfusions of whole blood, eradication of all local foci of infection present, laparotomy for removal of the spleen and other tissues showing evidence of chronic infection. Even though no ultimate cures may result, it seems that the work is worth while; that it offers at least the quickest and most certain method of obtaining a remission of the disease, even in some of the extreme and long standing cases.

THERAPEUTICS

UNDER THE CHARGE OF

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A Study of Ethylhydrocuprein (Optochin) in the Treatment of Acute Lobar Pneumonia.—MOORE and CHESNY (*Arch. Int. Med.*, 1917, xix, 611), in a comprehensive article, discuss the action of optochin as observed experimentally and also clinically. As judged from a series of 32 cases, when optochin hydrochloride was given by mouth to patients suffering from acute lobar pneumonia in such amounts that they received at least 0.024 gm. per kilogram of body weight per twenty-four hours, and when the size and spacing of the individual doses were adequately regulated, a specific pneumococcidal action appeared in their blood within a few hours, and could be maintained more or less constant for several days. In order to maintain the bactericidal action in the blood at a constant level, the intervals between the individual doses given by mouth should not ordinarily exceed about two and a half to three hours. When optochin is given by mouth according to such a scheme of dosage as outlined, the evidence points to some retention or accumulation in the blood of part of the drug absorbed. Administration of optochin hydrochloride by mouth appears to be more satisfactory than intramuscular administration. Further study of intramuscular administration appears to be desirable. Pneumococci not only *in vitro* but also in the human body in patients treated with optochin, may acquire the property of more or less complete resistance or "fastness" to the drug Toxic symptoms, such as tinnitus, deafness, amblyopia, or amaurosis (retinitis) may be observed in the use of the drug in man; they are generally transient. Retinitis, however, may result in more or less permanent impairment of vision.

The Effects of Salicylates on Experimental Arthritis in Rabbits.— FANTUS, SIMMONS and MOORE (*Arch. Int. Med.*, 1917, xix, 529) found that sodium salicylate, when used in a dose comparatively harmless to animal controls is decidedly detrimental and liable to be fatal to animals infected with the hemolytic streptococcus. The addition of sodium bicarbonate does not lessen much the harmfulness of the salicylate to infected rabbits. Sodium bicarbonate given alone is not

injurious to infected rabbits, neither does it produce a noticeable improvement. Acetylsalicylic acid in equivalent dosage appears to be much more toxic to normal rabbits than is sodium salicylate, and is harmful to infected rabbits as well. Salophene has either no influence or an unfavorable one on the course of the infection. The results of the experiments reported point to the conclusion that in the experimentally induced arthritis of rabbits salicylates are not only worthless, but even harmful. To bring these results in harmony with the clinically established usefulness of salicylates in rheumatic fever in human beings, several possibilities must be considered: (1) The Streptococcus hemolyticus used in these experiments might not have been the strain of streptococcus that is particularly susceptible to salicylate. It is well known that not all cases of infectious polyarthritis respond to salicylate in a specific manner; (2) it might be that there is a chemical difference between the system of the rabbit and that of man in its relation to salicylate; for example, a difference in the hydrogen (ion) concentration of the tissue fluids; (3) the action of salicylate in human beings might be merely symptomatic, but not really curative.

The Treatment of Tuberculosis with Cyanocuprol.—OTANI (*New York Med. Jour.*, 1917, cv, 537) says that cyanocuprol has been shown to be effective in cases of tuberculosis of varying degrees of severity. Of 22 patients that seemed to be hopeless and had been treated with all known methods, 8 showed marked improvement. The size of the dose seems to be closely related to the symptoms and the reactions. During the first period, when larger doses were employed, less beneficial results were obtained than during the second period when the size of the dose was considerably decreased. Cyanocuprol is effective in cases with fever, malnutrition, induration, and catarrhal condition of the lesion. In pulmonary tuberculosis the dull area and rales usually decrease, the number of bacilli in the sputum is diminished. The author has not yet studied a sufficient number of other forms of tuberculosis to permit any conclusions to be drawn. Injections of cyanocuprol sometimes causes general or lesional reactions in the patients. Febrile reactions were observed in 14.6 per cent. and lesional reactions in 25.6 per cent., based on the number of injections. These reactions were slight and transient. More severe reactions were produced in only 6.4 per cent. of the cases. During the first period in which the author had only a limited experience in the use of the drug, 7 cases showed unfavorable results; but during the second period there were none. The present communication is an additional contribution on this same subject, and the author now reports a total of 118 cases of tuberculosis treated on this plan during the past year.

The Nutritional Value of the Banana.—MYERS and ROSE (*Jour. Am. Med. Assn.*, 1917, lxviii, 1022) say that bananas have a higher caloric value than any of our other common fruits. Unlike most other fruits, they are always in season. When fully ripe, that is, when the starch has been almost completely changed to sugar, the experiments here reported show that the carbohydrates of the banana are well absorbed from the intestine. As sold in the market, however, bananas are frequently not sufficiently ripe to be consumed to advantage

immediately, and it would seem that gastro-intestinal disturbances when attributed to the banana were referable to this cause. It may be said, in general, regarding the experiments of the authors, that no ill effects, discomfort, or distaste were noted even after the consumption of large quantities of sugar (glucose, sucrose, levulose) may be given in the form of banana than as pure sugar (sucrose, glucose) without producing gastro-intestinal disturbances. The composition of the banana and the potato shows an interesting similarity both as regards total carbohydrate and the amounts of the different mineral constituents. While the banana can hardly be regarded as a potato substitute, the fact that it has practically the same caloric value as the potato is worthy of note. It is also of interest that both the banana and the potato yield an alkaline ash and are therefore antagonistic to the development of an acidosis. Of even greater importance is the fact that bananas may be eaten uncooked. This is of interest in view of the increasing significance that is being attached to the thermolabile "accessory food substances." The banana would appear to be a particularly valuable food to employ in the dietetic treatment of nephritic patients with nitrogen retention. Very satisfactory results have been obtained in the rather mild cases of nephritis here reported. As long as the patients exhibit no distaste for the fruit, there would seem to be no reason why bananas should not be employed in considerable quantity. The authors hope to report in the near future results obtained with this form of diet in cases of advanced nephritis.

Salvarsan and Neosalvarsan in Syphilis.—ORMSBY (*Jour. Am. Med. Assn.*, 1917, lxviii, 949) is of the opinion that salvarsan and neosalvarsan are the most efficient drugs yet discovered in the treatment of syphilis. Alone they have completely eradicated the infection in early cases before the Wassermann reaction has become positive. The large number of reinfections testify to this fact. Yet even in these cases mercury is recommended as an adjunct. In all other cases, mercury should always be an accompaniment of salvarsan, and in many cases potassium iodide is indicated, especially in the so-called tertiary and latent cases and in those involving the nervous system. The ability of potassium iodide to remove infiltrations, gummas, and nodules, together with its marked effect on vascular implications, renders its use imperative. The major number of reactions following the use of salvarsan and neosalvarsan are insignificant. The more serious ones are to be avoided, so far as possible, by an initial small dose to test the tolerance of the patient, by careful attention to details in administrative technic, by recognizing contra-indications, and, in the case of early, active syphilis, preceding the salvarsan treatment with mercury, to prevent neurorecurrences; and finally by giving sufficient treatment to control the disease. The author lays emphasis on the latter statement, as much harm may be done by its apparent effect, the degree of relief placing the patient in a position of false security; therefore sufficient treatment is demanded to prevent recurrence and relapses. Many of the earlier cases, following insufficient treatment of rapid onset of symptoms which ordinarily come late in the disease, such as nervous involvement and precocious tertiary manifestations, were eradicated by more salvarsan, and now should be entirely

avoided by treatment of sufficient intensity and amount to control the disorder. The treatment of syphilis with salvarsan and neosalvarsan has caused an intensive study over the entire world of the question of efficient management of the disease, to such a degree that great lessons have been learned and much good accomplished. Their ultimate value will require many more years to determine as to a choice between the two drugs salvarsan and neosalvarsan, the extensive use of both proclaims their efficiency, so that individual circumstances with the physician and patient must decide which, under the circumstances, is to be selected. The apparent preponderance of opinion that salvarsan is more efficient is offset to a degree by the difficulties of its administration and the more frequent reactions following its use. Concerning the dangers following the individual injections, many warnings have been given to exercise care after the fourth injection. The warning has not been accompanied by tabulated results, showing proof of this contention. On the other hand, the statistics now available show that the major portion of severe reactions, untoward results and fatalities have followed the first injection, and that with subsequent injections these results were greatly decreased.

The Transfusion of Blood.—McClure and Dunn (*Bull. Johns Hopkins Hosp.*, 1917, xxviii, 99) give a brief summary of the history, various methods, necessary precautions and dangers of blood transfusion. They have given 150 transfusions to 80 patients and a tabulated summary of the cases so treated is included in the article. The authors have used transfusions in the following conditions: pernicious anemia, illuminating-gas poisoning, exophthalmic goitre, hemophilia, toxemia, shock, hemorrhage, leukemia, septicemia, purpura hemorrhagica, malnutrition, endocarditis, intoxication, general debility, dysentery, typhoid fever, infectious diseases, melena neonatorum, scarlet fever, pellagra, tuberculosis and tumors. It has also been used for vaccinating purposes. The best results have been obtained in hemophiliacs and babies with melena neonatorum; in the latter it is a specific, and in the former it stops the bleeding immediately, although without curing the disease. It is of great benefit in all anemias and with proper regulation may be of still more benefit in the primary types. Thus far, in shock it has been disappointing. This may be due to the fact that the shock has progressed too far before the transfusion has been done. They would advise a very early transfusion in cases of shock. Following acute and prolonged hemorrhage transfusion is of the greatest benefit. For gas poisoning, bleeding is beneficial, as was pointed out by Halsted. Depletion followed by injections of saline solution is as good, if not better, than transfusion. In tuberculosis there has been only slight benefit and so far, nothing has been accomplished by transfusion in malignant diseases in man. They believe that there is a great field to be developed in the line of vaccinating transfusions. Their experiences in typhoid fever have been very satisfactory. It would be very desirable to have a series of donors who have recently had typhoid fever ready to give blood to very ill typhoid patients. In one patient, depleted by hemorrhages as well as having a high-grade toxemia, the transfusion of blood, from a person who had previously had typhoid fever, brought about the most marked

improvement, the temperature dropping to normal and the hemorrhage ceasing, with a temporary disappearance of the toxemia. This is very suggestive of the good that might be accomplished by transfusing typhoid fever patients with blood from patients who have recently had the disease and who have probably a high grade of immunity. It would be interesting to try this type of transfusion in patients with other diseases and the procedure might prove very beneficial. A severe reaction occurred in 20 cases; a slight reaction in 25 cases; a chill in 15 cases; temperature elevation of over 101° F. in 34 cases; hemolysis in 8 cases. The results are summarized as life saving, 15 cases; beneficial, 63 cases; no benefit, 56 cases and harmful, 16 cases. Two deaths were probably due to transfusion, certainly one death was due to the improper matching of the blood.

The Passage of Neutralizing Substances from the Blood into the Cerebrospinal Fluid in Poliomyelitis.—FLEXNER and AMOSS (*Jour. Exper. Med.*, 1917, xxv, 499) report that the cerebrospinal fluid taken very early and quite late in the course of acute poliomyelitis exhibits no neutralizing action on filtered poliomyelitic virus. The blood serum on the sixth day of the disease already contains the neutralizing principles. The injection of sterile horse serum into the cerebrospinal meninges in monkeys increases their permeability, so that they permit the immunity neutralizing principles passively injected with the blood to pass into the cerebrospinal fluid. The passage in passively immunized monkeys takes place during a relatively brief space of time and apparently only while the inflammatory reaction produced by the horse serum is at its height. It is established for monkeys and rendered probable for man that the intraspinal injection of immune serum in poliomyelitis is curative. In monkeys normal serum exerts no such action, and at present nothing can be stated definitely regarding the therapeutic effect of normal serum in man except that probably any benefits which may arise from its employment would be attributable not to the action of the serum as such, but to the escape of circulating immunity principles in the blood made possible by the aseptic inflammation set up by it in the meninges. As the immunity principles appear in the blood only after several days, and the reported favorable effects of the immune serum treatment relate to the first days of illness, the employment of normal serum is thus not indicated, while that of an immune serum is.

Lumbar Puncture for the Relief of Delirium in Lobar Pneumonia.— MUSSER and HAFFORD (*Jour. Am. Med. Assn.*, 1917, lxviii, 1231) report seven cases of pneumonia associated with severe delirium, in which relief of the delirium promptly followed lumbar puncture. The mortality rate was high, but as delirium is usually an indication of a severe infection, the authors feel that lumbar puncture offers a ready aid in controlling one of the symptoms which may so aggravate the patient's condition that what little chance he may have of surviving the infection would be lost were it not for this procedure. Lumbar puncture is, therefore, suggested as a measure to control a severe symptom, and not for any direct curative purposes.

OBSTETRICS

UNDER THE CHARGE OF

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Morphin-scopolamin during Labor. — GREENWOOD (*British Med. Jour.*, March 17, 1917) reports his experience in 150 cases of labor treated by morphin-scopolamin. But 2 cases failed to respond and showed no amnesia. These were patients in their own houses, multiparæ, who were not seen until labor was well advanced and in whom labor terminated very promptly. The writer thinks that it is vitally necessary that the physician be in constant attendance because morphin-scopolamin acts so variously upon different patients. There is no way of foretelling how many doses will be needed or how frequently. A routine method of treatment cannot be established. The time occupied in producing amnesia varies greatly and in these cases was from twenty minutes to four hours after the first injection. There were a number of abnormalities among the cases including three with mitral lesions and three with very marked albuminuria. These did well. There were 3 cases of postpartum hemorrhage in multiparæ who gave a history of having had this in previous labors. There was no maternal mortality among these patients and an infant mortality of 2 per cent., in which it could not be determined that the treatment had any influence upon the result. In 15 per cent. of the infants there was some interference with respiration. The study of the cases shows that to avoid interference with the infant's respiration morphin should not be given too late in labor or if it is necessary to use it, the dose should be progressively decreased. The best results are obtained when the treatment is begun early as soon as labor is definitely established. There seems to be no real delay in labor because of this treatment. The mother showed remarkable absence of exhaustion and shock. If this treatment is used to secure amnesia and not analgesia the writer believes that it has no danger for mother or infant. If pushed beyond this limit, the risk may be grave. To be used safely, the obstetrician must be constantly watchful during the labor. In over 50 per cent. of mothers the pulse-rate was considerably altered although the pulse showed no signs of weakness. The writer also states that among these patients were some who had positively refused to have a child because of the dread of physical suffering. By the use of this method, they were safely delivered without injury or pain.

Pyelitis in Pregnancy and Parturient Women.—GAMMELTOFT (*Ugesk. f. Laeger*, Copenhagen, January 18, 1917) has found in his experience that in its beginning pyelitis among pregnant women may simulate other intra-abdominal diseases. Cases run a very different course which also increases the obscurity of diagnosis. The colon bacillus is the cause of the disease in 70 per cent., and as pregnant women suffer habitually from constipation and often have disturbances

of the gastro-intestinal tract the occurrence of colon bacillus infection is readily explained. In its acute form the disease may declare itself quickly with general depression and fever and with or without a chill. It is common to observe nausea and vomiting in these cases. The patient may imagine that she is in the first stage of labor because the pains suggest labor pains. Usually after a time pain becomes localized in the kidney region, usually the right, occasionally in both. The ureter and bladder may be the seat of pain and tenderness. In the iliac fossa there may be considerable tenderness while at the symphysis there is very little or none. The urine is turbid and acid reaction. It has a putrid odor suggesting colon bacillus infection and albumin is sometimes present. On examination of the urinary sediment with the microscope usually a clinical diagnosis can be made without a bacteriological examination. In rare cases the urine is apparently normal because on the affected side the ureter has become blocked and only urine from a sound kidney is available for examination. The temperature fluctuates, often rising to 104–105. There are occasionally severe chills. The general condition usually remains good and the pulse is very little disturbed. If the case receives treatment, in about ten days the acute stage passes and the chronic follows. After the acute stage while the most significant symptoms of the disease may be lacking, the patient will complain of pain in the lumbar region and frequent desire for micturition. With these patients the urine should be examined thoroughly and if necessary cultures should be made. In pregnant patients it may be very difficult to ascertain exactly with what one is dealing. The pain and distress from which these patients suffer very closely resemble that cuased by appendicitis. Cystoscopy and catheterization of the ureters will often clear up the diagnosis. In treatment, rest in bed, moist heat over the painful area, and copious drinking of milk, lemonade, boiled water and weak tea are useful. Urotropin has given good results. In uring urotropin as much as 50 centigrams every four hours have been administered. Should there be retention of urine it may be necessary to catheterize the ureter at comparatively short intervals. It is best not to inject fluid into the kidney. Considerable help is seen in some cases by posture, turning the patient on the side opposite the infected kidney, when pressure upon the ureter will be relieved and the urine be discharged freely. Rinsing out the bladder is also useful and greatly relieves spasmodic pain. When the patient is convalescing, salol is often useful. An autogenous vaccine is thought to be valuable to prevent recurrence. .The bacteria may be present in the urine for a long time after an attack and may change in their potency and development.

Cases of Apparent Appendicitis Complicating Pregnancy.—Van Trim (*Annal. de Gynec. de Obstet.*, 1916, xlii, 177) draws attention to the occurrence of symptoms in pregnant women precisely simulating those of acute appendicitis. In the first a gangrenous diverticulum was found at operation while the appendix was normal. In two other cases the symptoms were caused by suppurating dermoid ovarian cyst. The fourth patient had classic signs of sudden pain in the right lower abdomen but at operation the cecum and appendix were healthy. A collection of blood was found extending into the iliac fossa behind

and below the uterus and broad ligament. The case proved to be one of intra-uterine pregnancy and also ruptured tubal pregnancy. The fifth case was postpartum and the symptoms were caused by the twisted pedicle with partially suppurating ovarian cyst. It is not uncommon in parturient and puerperal women to have bilateral pain described in the lower abdomen. Occasionally this pain is unilateral and can often be traced directly to the region of the ovary. In some patients this pain follows nervous or psychic shock and is attended by no physical symptoms. In making a differential diagnosis the obstetrician should remember that young women may have an acute infective process with normal temperature and without rigidity of the abdomen, the cardinal symptom being high leukocytosis and the complaint of pain. This pain may occur periodically and may strongly simulate the pain of hysteria. Great help is obtained in diagnosis by the examination of the blood to determine the degree of leukocytosis present and the bacterial examination of the urine to determine the presence or abscess of colon bacillus infection of the kidney. Two cases in the experience of the reviewer illustrate this point. In the first, a young woman with a normal temperature was suffering from infection following a criminal abortion. She had no rigidity of the abdominal muscles and slightly subnormal temperature and rapid pulse. There was a foul discharge from the uterus. On admission to the hospital her condition was so grave that operation could not be performed. An autopsy rupture of the pyosalpinx and acute infection of the peritoneum were present. In a second case a young woman had produced upon herself abortion by inserting a slippery elm stick. She had a normal temperature, not much abdominal rigidity but complained periodically of severe abdominal pain. Her leukocytes were above 21,000. The pain was so pronounced and came so regularly that it seem hysterical in character. On section both Fallopian tubes exuded pus, the general peritoneum was injected, the appendix was normal. This patient did well with drainage of the pelvic cavity.

Morphin-hyoscin Method of Painless Childbirth.—HAULTAIN (*British Med. Jour.*, October 14, 1916) states that the method of Krönig and Gauss had not been accurately followed by the majority of the British obstetricians who have used the drugs. In the Royal Maternity Hospital in Edinburgh, Haultain and his staff rigidly adhered to Krönig's technic in the first 8 cases and the results were satisfactory. He observed that patients sometimes became restless and highly excitable and this seemed to be a personal peculiarity of the individual case. With some patients more than twenty-two injections were given during labor. Where it was impossible to obtain separate rooms for the isolation of the patient, the ward was darkened and screens placed about the patient's bed and cotton placed in the ears. Forty cases were so treated, 36 primiparæ and 4 miltiparæ. Smallest number of injections was four and the greatest forty-five. Usually $\frac{1}{4}$ grain morphin was given at the beginning with $\frac{1}{150}$ grain hyoscin. In 3 cases $\frac{1}{6}$ grain morphin was first used. In 3 cases morphin was repeated and the second dose was $\frac{1}{8}$ grain. In 30 out of 40 amnesia and analgesia were obtained. There was some effect in every case. In 3 cases the method failed. In 1 case there was marked restlessness

and injections had to be stopped. Postpartum hemorrhage occurred in 1 case and in 14 patients the forceps had to be applied. In 5 of these the instrument was used without chloroform and in the others chloroform was given. Of the 40 children, 5 were dead born, and of the 35 born living, 4 required artificial stimulation. In using the method in a primipara the first injection must not be given too early as it tends to stop the pains. When the os admits two fingers and pains are regular the drugs may be employed. In a multipara the injections can be begun as soon as labor starts. The second injection, $\frac{1}{150}$ gr. hyoscin should be given about one hour after the first injection and this can be repeated at intervals of one hour or three-quarters of an hour afterward. The morphin should not be repeated in the later part of the second stage because it tends to produce asphyxia in the child. The advice is given that if the hyoscin is not taking effect, it is well to give the mother a slight whiff of chloroform. Thus the hyoscin is allowed to work and the patient passes into the condition of "twilight sleep;" 37 of the 40 patients got up out of bed on the third day after labor. We are somewhat interested to observe that the writer describes the administration of morphin hyoscin as the method of Krönig and Gauss. They employed scopolamin and laid great stress upon the absolute purity and quality of this drug. There is nothing new in the employment of hyoscin with nervous patients whether they be pregnant or not and morphin has long been known to be useful with nervous patients during labor. The suggestion to give chloroform to permit the hyoscin to take effect is an extraordinary method of treatment and one which does not appeal to us. We do not observe that the results of this treatment were specially satisfactory in avoiding the use of forceps, and yet it is supposed that if the patient be spared suffering her strength will be conserved and the use of forceps will be reduced to a minimum. After being extensively exploited by the public press and after a determined effort had been made to make the scopolamin method popular with the public, it has passed into the category of medical nostrums of doubtful value. The only benefit to the public and the profession which its attempted introduction produced was the study of the best and safest methods of lessening pain during labor and this brought out clearly that the scopolamin morphin method was difficult of application, uncertain in results frequently producing asphyxia in the child, lengthening labor and much inferior to other reliable and safe methods of treatment.

Joined Twins.—Iyer (*Indianapolis Med. Gaz.*, 1916, li, 237) reports the case of a woman who had been in labor three days. On examination a fetal head and left forearm had been delivered. A second head with its face turned toward the delivered one was also found. This could not be pushed up so was delivered with forceps without much difficulty. Both children were removed through the uterus and a common placenta was expressed shortly afterward. On examination it was found that the twins were attached by the cartilage of the ribs. There was a common abdomen covered only by peritoneum but there were separate pelvic bones and pelvic organs. There was one cord and one liver and spleen. There were two pairs of kidneys, a single heart, one diaphragm and two lungs.

The Combination of Morphin and Pituitrin in Labor.—Olivella and Arteaga (*Rev. med. de Sevilla*, 1916, lxvi, 1916) in 7 cases reported good results by using a combination of the hydrochlorate of morphine and extract of the fresh pituitary body and a sterile vehicle. Pain was greatly diminished, uterine contractions were better and the general condition of the patient remained good. Postpartum vomiting occurred in 1 case only and involution was normal. One child was born apneic but was readily revived. The children seemed stupid and breathed languidly during the first twenty-four hours after birth and required special care.

GYNECOLOGY

UNDER THE CHARGE OF

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Surgical Traumatism as a Cause of Recurrence in Uterine Carcinoma.—Facts well known to every scientifically trained surgeon, but often not sufficiently kept in mind or acted upon, are well brought out in a paper by Shoemaker (*Am. Jour. Obst.*, 1917, lxxv, 758). He points out that it has been conclusively shown by Bloodgood, that in carcinoma of the breast the chance for recurrence is so increased by a preliminary excision of a specimen that permanent cure practically never occurs in cases where a piece of tissue has been excised for microscopic study and radical removal is not immediately carried out. Since it can be shown experimentally that tumor cells can enter vascular channels and be transported to a new radius of development, can anyone doubt the enormous importance of avoiding all squeezing of new growths accompanied by punctured wounds, such as occur in the use of double tenacula? No one would think of doing this with other malignant tumors, yet it has been customary with the uterus. The time required for any given blood corpuscle to circulate from the periphery to the heart and back to the periphery again has been estimated at from fifteen to twenty-three seconds. The time occupied between the start of a cell from a carcinoma, once entered the blood stream, to the heart and out to some peripheral point must therefore be calculated not in hours, not even in minutes, but in *seconds*, so that there is no time for operative excision to secure safety. For the time being, one may put aside the question as to what factor causes cancer; it is sufficient for this argument that where cancer cells are transferred in the blood stream they form under proper conditions a new nidus of the disease. The bearing of this upon the clinical study of a possibly malignant condition of the uterine cervix is obvious. In order to see, at times the temptation to use a tenaculum is very great. While inconvenient, however, a grasp may frequently be obtained outside the diseased area, and this should always be done, or the tissue grasped should first be cauterized. If unable to avoid making a preliminary microscopic

diagnosis (and this can be avoided in the large majority of cases), never excise a specimen except with the cautery knife, and for immediate diagnosis and immediate operation. Use no hooks! Obtain microscopic confirmation afterward if possible, but do not in the presence of clinical probability produce dissemination in a patient of cancerous age by surgical traumatism of an uncauterized growth.

Operation for Uterine Prolapse.—A novel and rather remarkable operation for the relief of bad cases of prolapse is described by HELMUTH (*Ann. Surg.*, 1917, lxv, 469). It consists in opening the abdomen by the usual vertical median incision, and then separating the adnexa and round ligaments from the uterus, as though a supravaginal hysterectomy were to be done without removing the tubes and ovaries. The uterine body is thus freed of all attachments down to the point of bladder reflection; the broad ligaments are whipped over exactly as after a hysterectomy, but the uterine body instead of then being cut away at the internal os is split sagitally from the fundus down to the level of the bladder attachment. The median incision in the fascia is now closed, and a short veirtcal slit, about a half inch in length, is made through the fascia and peritoneum on each side of the median incision, and parallel to it. Each half of the bisected uterus is now brought out through one of these slits, the fundus of the uterus being then sewed together again above the fascia, which thus runs through the uterine body between the cervix and fundus, keeping the latter permanently outside the fascial layer of the abdominal wall. The skin is then simply closed over the projecting uterine fundus in the usual manner. The author says that he has been able in this way to hold up permanently the prolapsed uterus better than by any other method he has used. If the cervix is large and hypertrophied, as is usually the case, it is amputated from below in the usual manner before opening the abdomen.

Hernia of the Bladder.—An unusual case of involvement of the bladder in an incarcerated femoral hernia has been reported by SALIBA (*Jour. Am. Med. Assn.*, 1917, lxviii, 1237). The patient, a woman, aged fifty-four years of age, was admitted to the hospital with a history of vomiting and obstipation with abdominal pain for four days. Examination showed a globular lump, the size of a small hen's egg, below and to the outside of the right pubic spine. It was hard, tense, tender, dull, and completely irreducible. On making an incision over it, and locating the sac, clear amber-colored fluid escaped as soon as the latter was injured. This was soon determined to be urine, and it was evident that the bladder formed part of the sac contents, and was adherent to it at the point of opening. The bladder injury was carefully closed, and dissected free from the sac wall. There was also a loop of intestine in the hernia, the strangulating agent in which was found to be not Hey's ligament, but the mouth of the sac itself, which was found to be greatly thickened. In dividing this thickening the bladder was again accidentally wounded, and was again sutured, after cleansing the wound with ether. The operation then proceeded in the usual manner, and has resulted in permanent relief of the hernia. No drainage was used.

PATHOLOGY AND BACTERIOLOGY

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Concerning Renal Sclerosis.—What at one time appeared a very happy agreement between several authors on Bright's disease (Jores, Loehlein, Fahr) has now resulted in confusion wherein each of these men stands by himself for a separate theory of the disease. Jores can see but one factor underlying the development of renal sclerosis and that is arteriosclerosis. To him the tissues of the kidney other than the arteries appear to play only a passive role and give evidence of morphological and functional disturbance in proportion to the arterial lesion and its effects upon the circulation. He gives no clear view in what manner the development of the benign fibrosis of the kidney differs from that of the malignant. Loehlein broadly agrees with the views of Jores. He recognizes the two types of renal sclerosis, but appears to regard the malignant one as nothing else than an advanced stage of the benign. He takes it that it is only a matter of the extent of the involvement rather than a difference in kind. For the determination of the injury resulting in the kidney from these arterial lesions attention is particularly attracted to the glomerular changes and the degeneration of the tubules. FAHR (*Cent. f. Path.*, 1916, xxvii, 481), on the other hand, although considering the vascular lesion as essential and primary, believes that another factor must be superimposed for the production of malignant fibrosis of the kidney. As to the nature of this added factor he has little to offer definitely. This type of kidney disease with a dual etiological factor he prefers to speak of as the "combination type." His descriptions of the actual changes occurring within the kidney are very similar to those long ago described by Gull and Sutton. None of the authors appear to be familiar with the early work of Councilman, and although all of them recognize the common arterial lesions in interstitial nephritis they appear to lay no stress in their studies upon the causes of these processes. It would appear that no useful purpose is to be attained through the polemic by these authors as long as they make the subject of their controversy a late incident in this important disease.

Diminution of the Number of Islands of Langerhans in Diabetes.—Various authors have claimed that there is a definite diminution in the number of islands of Langerhans in diabetes. In 1900 Ssobolew

claimed to have observed the complete absence of island structures in 2 cases, while later he found 4 others with a similar condition. In 9 he noted a definite diminution in the number of islands but as he did not study portions of tissue from different parts of the pancreas, it is impossible to lay much stress on his observations. Subsequently Weichselbaum observed the unequal distribution of the islands in the pancreas in normal individuals and found that these structures are always more common in the tail than in other parts. Similar observations were made by Opie and Cecil. Martius examined a series of 27 cases of diabetes and was unable to support the contention that there was any relationship between the number of islands found and the occurrence of glycosuria. In these analyses portions were obtained from various parts of the pancreas and an estimate of the number of islands was made in a constant area of 0.5 square centimeter. Although the number of islands in a few cases was less than normal, it was claimed that a larger proportion of cases of diabetes showed no comparable change. Martius laid more stress upon the presence of morphological changes in the islands than upon an actual diminution in the number. Recently HEIBERG (*Cent. f. Path.*, 1916, xxvii, 49, and *Arch. f. Kinderheilkunde*, 1916, lxv, 388) carried out similar studies upon the relationship between the numbers of islands and diabetes. He divided the cases of diabetes into two groups: (1) Those showing pathological changes in the islands only; (2) those with wider involvement. It is the first group which particularly attracts attention and of which it is so commonly stated that true clinical diabetes was present without definite pancreatic lesions. In this group, it is found that a certain number of cases show definite island lesions which although not involving all of these secreting structures, materially interferes with function. When hyalin and other degenerations are observed the diagnosis of the pancreatic affection is not difficult. But in those cases where the island lesion has led to the disappearance of many of them and where the remaining ones appear normal or even hypertrophied, it is difficult to point to the damage in the pancreas as associated with diabetes unless a numerical diminution in the number of these structures can be determined. In an analysis of 12 of his own cases along with a group of others taken from the literature he claims to have established definite evidence showing a decrease in the number of islands. These analyses were made by careful counts in sections taken from various portions of the pancreas. When compared with observations upon the normal pancreas it is shown that this diminution is fairly constant. The author also reëstablishes the tables compiled by Martius and shows that this author obtained the same results. Heiberg, furthermore, finds that a similar diminution in the number of islands may be demonstrated in the pancreas of children ill with diabetes.

Studies of the Betahemolytic Streptococci.—The relation between scarlet fever, streptococci and septic sore throat is a subject which has always been very puzzling to investigators. Septic sore throat has been proved by many observers to be due to a type of streptococcus named by Smith and Brown, β-hemolytic streptococcus. Scarlet fever although so commonly associated with streptococci has not been

proved to have any direct relationship to this organism. SMILLIE (*Jour. Infect. Dis.*, 1917, xx, 45) reports a study of three epidemics of septic sore throat, in some of which the relation between scarlet fever and this condition is very suggestive. One epidemic occurred in the town of Dorchester among customers of a certain dairy. Although three farms supplied milk to this dairy and sources of β-hemolytic streptococci were found in each, one employee of one of the farms had a history suggestive of an attack of scarlet fever just previous to the outbreak of the epidemic. The second epidemic was in a boys' boarding school where 17 cases of septic sore throat occurred. The milk used by all these boys was found to have been insufficiently pasteurized, and the examination of the cows from which the milk was obtained showed the presence of this type of streptococcus in one of them. No cases of scarlet fever were found in this outbreak. The third epidemic occurred in a hospital and was proved to be a combination of milk-borne and contact infection. Another interesting group of cases was also found by this observer. Three small girls who played together on a Monday afternoon, all became ill on Thursday of the same week. One developed a typical case of scarlet fever. The second a very mild case of the same disease, while the third developed a very severe septic sore throat but showed no skin rash nor any other sign of scarlet fever. β-hemolytic streptococci were found in the throats of all three girls. In careful bacteriological studies of all of these cases both during the disease and convalescence and also in studies of normal throats, the author found β-hemolytic streptococci so frequently that their importance in septic sore throat appears established and in scarlet fever is a matter not to be considered too lightly. The organism is one which grows in variously sized chains, shows some capsular substance and on blood-agar causes a very wide hemolysis around each colony, this zone sometimes being 5 mm. wide. The carbohydrate reactions as given in this paper are not particularly valuable. Cultures on carbohydrate medium were titrated for quantity of acid and this has been proved by Broadhurst, and also by Holman to be a method, the results of which vary with many factors such as medium, vigor of growth, etc. From the results of the carbohydrate fermentation given by the author this streptococcus would come under the head of Streptococcus infrequens in the classification of Holman. This streptococcus has been found by a number of other observers in the throats of scarlet fever patients and has been easily recognized by them by means of its hemolysis and also by its characteristic carbohydrate reaction. The fact that it is not a frequent inhabitant of normal throats and occurs almost always in the above mentioned conditions is, as the author states, very suggestive of the relationship between these two diseases and the danger to a community of the presence of either of them.

Observations on the Mode of Origin of the Fibro-adenoma of the Mammary Gland in the Rat and on the Delayed Retrogression of the Mammary Gland after the Period of Lactation.—In the report of a study of four curious neoplasms in the breasts of a female rat, LOEB (*Jour. Cancer Research* 1916, i, 415) offers some interesting suggestions on the mode of origin of fibro-adenomata in these animals, and

on the condition resulting from delayed retrogression of the mammary gland following lactation. Admirable microscopic descriptions of the tumors are given. One resembled, in the gross, an ordinary fibroadenoma. In sections, however, the character was that of a recently functionating mammary gland, within some areas vacuolated cells in acinar arrangement and a well-developed stroma. In a few places there was a relative increase in epithelial elements, as though the stroma had been reduced in amount. The author concludes that the failure of normal retrogression is the cause of fibro-adenomata in the breast of the rat. In this connection he gives no hint that growth of fibrous tissue had occurred, nor that epithelial elements had proliferated. Nor is there any indication that the growth was encapsulated, but rather one is led to infer that the whole breast is considered a tumor. This entails a special classification of tumors for the rat. The writer invokes a special local condition of unnamed sort to account for the reaction in this breast, but rules out infectious processes. Here is drawn an unfortunate parallel between the subinvolved breast and hepatic cirrhosis. The writer establishes simultaneous development of connective tissue and epithelial elements as the picture in cirrhosis of the liver though in the next paragraph one finds him agreeing with Weigert in the view that "hypertrophic proliferation of connective tissue is invariably the result of primary destruction of epithelium," a contrary notion to that of Mallory that pure parenchymatous degeneration rarely stimulates fibrosis, which occurs only when the stroma has also been affected by the irritant. In view of these facts, one hesitates to so readily relinquish the factor of a local irritant, even possibly a bacterial one. The other three mammary glands proved to be enlarged due to a cystic degeneration of the breast tissue. All were of the nature of single large cysts, containing a thick yellow fluid, possibly autolyzed material. Microscopically, the cysts were lined by a low cuboidal epithelium, interrupted in places by areas where necrotic tissue was adherent over a base of granulation tissue. In the cyst wall are compressed epithelial acini, some of which are cystic. Many small cysts frequently are jointed to the larger cavity, with the result that papillomatous masses covered by epithelium, project into the larger cavity. The statement is made that the necrosing masses adherent to the cyst are cut off from the healthy tissue by the growth of the lining epithelium through such masses at the pedicle. As a cause for this degenerative process and necrosis some "general factor, delaying the normal retrogression of several glands" seems less inviting than the comparison barely mentioned by the writer between this process and the casting off of the normal placenta. The effect of an obliterative endarteritis, in cutting off nutrition, might well be considered. And there is no reason to suppose that this process could not go on in different glands at the same time.

A Study of Experimental Non-hemolytic Streptococcus Lesions in Vitally Stained Rabbits.—CECIL (*Jour. Exper. Med.*, 1916, xxiv, 739) records experiments on rabbits in which he injected both Streptococcus viridans and trypan-blue. The doses were various and were given at intervals. The lesions which he obtained were striking and it is to be regretted that he did not classify any of the streptococci used but included them all under the heading of that very large group known

as non-hemolytic streptococci. Three of his strains were obtained from cases of rheumatic fever and three from cases of infectious endocarditis. The trypan-blue staining was of great assistance in studying the lesions, particularly in regard to the source and fate of certain inflammatory cells which were found in the lesions. The lesions noted were joint lesions which began as mild exudative inflammations and progressed to very severe types with fibrosis and in some cases destruction of cartilages of the joints and also some destruction of the underlying bone. The lesions in all cases were similar to those found in the human under the same circumstances. Heart lesions, both pericardial and endocardial, were rather infrequent and irregular but myocardial lesions were common though not similar to those described by former observers. Liver and kidney lesions occurred occasionally but were not characteristic and could not be compared with the lesions in the human. The value of the use of vital staining in the study of inflammatory cells particularly in relation to the source of these cells is demonstrated in this work. The injection of vital stains, however, changes to some extent the cell picture of inflammations and the author notes that this point should not be overlooked in such studies.

A Contribution to the Epidemiology of Lobar Pneumonia.—SILLMANN (*Jour. Exper. Med.*, 1916, xxiv, 651) sums the findings of mouth, lung and blood cultures of pneumonia patients and also mouth cultures of normal individuals taken at the Hospital of the Rockefeller Institute during four years. The cultures were taken from patients during the disease and for various periods after recovery in an attempt to note the incidence of carriers in convalescent patients and also to note the average length of time after recovery that the virulent pneumococcus remained in the mouth. Although the incidence of the Types I, II and III, and III vary somewhat from year to year, I and II are always the most frequent types. Type IV does not vary greatly and is next in frequency. Type III gives the smallest percentage of cases in most reports. Types I, II and III remain in the mouth for varying lengths of time after recovery from disease produced by one of them as does also Type IV. Type IV is very frequently found in the mouths of normal individuals whereas the other three types are not so frequent under these circumstances. In the case of III which is the most virulent pneumococcus and which occurs in the fewest number of cases of pneumonia, the incidence in normal mouths is relatively large and Types I and II are quite infrequent. All the cases listed under "normal mouths" are, of course, cases which were not in contact with pneumonia patients. In the mouths of nurses, doctors and relatives of pneumonia patients who are in fairly intimate contact with the case, a type of pneumococcus is frequently found which corresponds to the type isolated from the patient's mouth or lung. It is in these individuals that Types I and II are found most frequently because they are the most frequent organism found in patients. As to carriers it was found that IV was widespread. Type III is not very frequent and Types I and II did occasionally occur in mouths of individuals in whom it was impossible to trace any instance of contact. From these figures it is evident that even though chronic carriers of the virulent types of pneumococci are rather infrequent the danger from contact carriers is not to be ignored.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Studies of the β-hemolytic Streptococcus.—SMILLIE (*Jour. Inf. Dis.*, 1917, xx, 45) states that the β-hemolytic streptococcus was found by Theobald Smith and J. Howard Brown to be the etiological agent in several milk-borne epidemics of septic sore throat. They believed the strain to be a human type, though it may be introduced into a cow's udder and produce a mild reaction. It has definite characteristics which distinguish it, and which have been described by Smith and Brown. Smillie repeated the work of these authors in the study of the epidemiology of two outbreaks of milk-borne septic sore throat. In each epidemic, the β-hemolytic streptococcus was found in the throats of the victims. In one epidemic, the same strain of streptococcus was found in the suspected milk. In the other epidemic, the β-hemolytic streptococcus was isolated from a mildly inflamed udder of one of the dairy cows. In order to ascertain the prevalence of the β-hemolytic streptococcus in normal throats, 100 average throats were searched for the types of streptococci present, and though many hemolytic streptococci were found, the β-hemolytic type of streptococcus of Smith and Brown was found but once. The throats of 20 individuals who had had milk-borne epidemic septic sore throat within two years were searched for the β-hemolytic streptococcus in order to estimate the prevalence of carriers of this strain. One carrier was found, a nurse who had had septic sore throat four months before. This nurse had later been the cause of a small contact infection epidemic of tonsillitis, thus illustrating the relation between the sporadic and epidemic mode of infection. The throats of 20 cases of sporadic tonsillitis were studied in order to ascertain the proportion of cases of ordinary tonsillitis due to the Smith streptococcus. Five of the 20 cases were found to be due to the β-hemolytic type of streptococcus. Finally, the prevalence of the β-hemolytic streptococcus was studied in 48 cases of scarlet fever. This strain was found in the throats of all the severe cases, and in some of the moderate and mild cases of the disease. There seemed to be a close relation between the severity of the disease, and the numbers and virulence of the β-hemolytic streptococci in the patients' throats. The same type of streptococci were also found in the aural and nasal discharges of four suspected carriers of scarlet fever. In all these diseases—septic sore throat, sporadic tonsillitis and scarlet fever—the β-hemolytic streptococcus was found in gradually diminishing numbers throughout con-

valescence, usually disappearing from the throat in ten to fourteen days. The author believes that epidemic tonsillitis, or septic sore throat, is not wholly due to the use of contaminated milk, but that it may be spread by direct contact. The β-hemolytic streptococcus is rarely found in normal human throats, and carriers are not common. Thus, though the flora from human throats frequently finds its way to the daily milk supply, milk-borne epidemics are not of daily occurrence. The great menace to the community is the convalescent case of septic sore throat, sporadic tonsillitis or scarlet fever, for this individual is a source of danger, insofar as he comes in intimate relations with his fellows; spreading disease to the individual by direct contact, or to the whole community by infecting the milk supply.

The Influence of Milk and Carbohydrate Feeding on the Character of the Intestinal Flora. Diet versus Bacterial Implantation.—
HULL and RETTGER (*Jour. Bact.*, 1917, ii, 47–71) remark that the culmination of several years of investigation carried on in the Sheffield Scientific School of Yale University corroborates the earlier experiments on animal feeding in which the following points were definitely determined. A change in the diet of white rats from the ordinary mixed food to one containing starch, lard, protein-free milk and a pure protein quickly led to a simplification of the intestinal flora, the Grampositive organisms being displaced by Gram-negatives. B. coli was practically eliminated, while members of the B. acidophilus predominated or constituted almost the entire flora. Milk and lactose were particularly effective in establishing the acidophilus group. In milk feeding B. acidophilus became abundant, while in continued lactose feeding it was usually supplanted by B. bifidus. Carbohydrates other than milk-sugar fail to bring about this transformation. The ingestion of foreign bacteria, even in large numbers, did not of itself bring about an elimination of the common intestinal microörganisms. The feeding of B. bulgaricus tablets without the use of milk or lactose can, therefore, be of little or no value. In the present investigation the following additional facts were obtained. Meat or other high protein diet increases the indol-producing bacteria and other organisms of the so-called "putrefactive" type, like B. coli and B. welchii; cornstarch appears to foster the amylolytic group of intestinal organisms, while in a few instances grain feed favored the development of what appeared to be fusiform bacilli. The reaction of the intestine remained independent of the character of the intestinal flora. While the acidity varied in the different rats, it was not increased during the lactose feeding. When lactose was given in dry form its presence could be detected in different parts of the intestine; during the feeding of lactose in solution the identification of the sugar in the intestine was much more difficult. The rapid development of the aciduric bacteria when a lactose diet is given in all probability is due to optimum cultural and environmental conditions which are created for these particular organisms by the lactose, although it may be present in very small amounts. A high lactose diet markedly influences the intestinal flora of man, though relatively large amounts of this sugar are necessary to bring about extensive changes in the flora. These facts have been amply corroborated by the work of other investigators. One

of the most important points established in the present work is the inability of a foreign organism to establish itself in the intestine of man or animal, except in disease by mere intestinal implantation.

The Clarification of Milk.—HASTINGS (*Jour. Am. Med. Assn.*, March 24, 1917, p. 899) states that careful experiments show that the bacterial content of milk is apparently increased by clarification, due to the breaking up of clumps. Clarification has no favorable effect on the keeping quality, and probably does not in any way improve the milk. It removes the dirt, but not the bacteria, pathogenic and otherwise, which were introduced with the dirt. It is hard to understand why health officials sanction clarification, yet the cities of St. Louis and Cincinnati, Ohio, Gary, Indiana, and Tulsa, Oklahoma, have passed ordinances requiring clarification, supposedly with the approval of the respective health departments. The introduction of pasteurization is opposed to by health officials because it enables the dealer to handle a poorer grade of milk than he otherwise could. Although this is, perfectly true, pasteurization gives the consumer a product more safe and of better keeping quality than the raw product. The clarification of milk is objectionable from the stand-point of the consumer, and yet health officials are apparently being led to urge its adoption.

Is Mosquito or Man the Winter Carrier of Malaria Organisms?— MITZMAIN and BRUIN (*Public Health Bulletin* No. 84, December, 1916, U. S. Public Health Service) studied the problem of quinin sterilization of the human host of malaria during the winter period; specially to determine: (1) If man alone harbors malaria parasites during this period. (2) If the mosquito is a potential factor in the perpetuation of malaria from fall to spring. The bulletin is an outcome of an intensive study conducted to determine for one locality at least, the relation of man and mosquito as influenced by the dormant conditions existing in the winter months in the southern United States. A group of fifteen plantations in the Mississippi Delta of the Yazo valley, having a known malarial index of over 40 per cent. comprised the district in which the investigation was conducted. At the outset, it was required to ascertain in what stage of its life history Anopheles mosquitoes existed. It was noted that for this region only intermittent hibernation prevailed and that the adult female mosquito was the only form observed to hibernate. It was ascertained during the course of the winter studies that in this region occasional biting of aroused Anopheles did not have any pathogenic significance, all of the infections clinically noted were proved to be recurrences of former attacks. It was concluded that hibernating anophelines collected in the region investigated, did not harbor parasites of malaria. This was determined after an examination of 2122 dissected anophelines, of which 1211 specimens were examined before May 15, 1915. Among the remaining 911 specimens, serving as a malaria indicator for the spring season, 3 mosquitoes between May 15 and May 26, were definitely shown to contain oocysts indistinguishable from those seen in mosquitoes experimentally infected with human malaria. In the investigation of man as the responsible winter carrier, 1184 persons, residing on the plantations selected, were examined for malaria parasites.

Four hundred and ninety-two infections were identified microscopically, 317 cases were of the subtertian type, 8 were mixed infections, and the remainder were of the simple tertian type, with the exception of one quart case. In the consideration of these infections an important fact stands out: nearly one-fourth (24.8 per cent.) of the human carriers harbored gametocytes. It was proved that from a group of 103 persons, examined in March, 1915, 8 of the 15 gametocyte carriers identified, were similarly infected during the preceding fall. The incrimination of man as the sole winter carrier is emphasized by the fact that 3 malaria infected Anopheles quadrimaculatus were found in the homes of the gametocyte carriers during May 15 to May 26, previous to which time 1180 specimens of anopheles from this source were found to be negative.

Laundries and the Public Health.—SCHROEDER and SOUTHERLAND (*Public Health Reports*, February 19, 1917, xxii, No. 6) state that the purpose of this study is to ascertain the methods employed in New York City laundries with special inquiry into the efficacy of such methods in destroying pathogenic bacteria and thus preventing the spread of disease. The survey includes the following: (1) Methods employed in handling clothes in the home. (2) Methods employed in handling clothes in the homes of laundresses. (3) Methods employed in handling clothes in the hand laundries (white and Chinese). (4) Methods employed in handling clothes in the steam laundries. (5) Series of special tests of goods to note the effect of heat upon bacterial life. (6) A canvass of steam laundry managers to ascertain their opinions concerning the use of nets in laundries. The authors found the methods of dealing with laundry in the home to be quite sufficient to make the danger from infected linen negligible. The laundry which is done in the home of a laundress is usually clean and free from bacteria; but owing to the close quarters in which the laundresses live, there is a possibility of reinfection of clean linen if communicable diseases are present among the members of the laundress' family. Of the so-called hand laundries, of which there are 2800 in New York City, there are three groups: (1) Laundries known as feeders for the steam laundries and maintained by them for sorting, marking or distributing. (2) Laundries operated by private individuals who do some washing and practically all the drying and ironing on the premises. (3) Laundries operated by private individuals practically doing on the premises all the washing and ironing for patrons. This group includes all the Chinese laundries. After a careful study of the location of and conditions in these laundries, the methods of sorting, washing, drying and ironing the clothes, the authors make the statement that the so-called "hand laundries" are, to some extent, a menace to the public health because of the crowded living quarters connected with the laundries; because of the probability of infectious diseases occurring among the persons living in such quarters without proper means of isolation; because of the careless method employed for sorting the clothes, allowing the contact of clean and soiled linen; because of the packing of nets with a heterogeneous mass of clothes which cannot be penetrated by the proper amount of wash water, and to which cannot be applied the proper degree of heat nor amount of disinfectants; and because of the

lack of proper facilities for drying and sorting the clothes, and the general insanitary conditions under which the work is carried on. The conditions in the Chinese laundries were, on the whole, better than those found in the laundries maintained by white people. In the investigation of the steam laundries, the methods were as follows: Bacteriological tests were made of: (1) The bactericidal strength of water plus the soap and disinfecting solutions and the possible mechanical elimination of large numbers of bacteria in the process of washing. (2) The penetrative power of the heat employed in washing. (3) The value of the ironing processes in the destruction of bacteria. (4) The value of the drying processes. Of the steam laundries in New York City there are several groups: (1) Laundries connected with infectious disease hospitals. (2) Laundries which deal directly with families or individual patrons, and in which the clothes are washed and finished. (3) Laundries dealing indirectly with families or individual patrons through the medium of hand laundries. (4) Wet-wash laundries. The methods employed in laundries connected with infectious disease hospitals are described separately and a review of these leads conclusively to the belief that pathogenic organisms are destroyed by these methods. From a study of the other groups included under the steam laundries the following conclusions were reached: The comparatively few steam laundries which use standard routine methods of washing and keep a record of the time, material and solutions employed are getting better results than the average establishments. The methods employed by steam laundries in the collection and delivery of clothes are insanitary—soiled and clean clothes being brought into close proximity. In the majority of laundries clothes are washed under conditions prejudicial to the health of the employees. The method, quite commonly employed, of returning "wet" clothes to the patrons and to hand laundries is a possible menace to the public health. Wet clothes infected with bacteria and subjected to the usual degree of heat in drying houses, "tumblers," mangles and hot presses are freed from living organisms. The practice of wet washing, as now done in steam laundries is insanitary as the clothes do not receive the proper application of disinfectants, soap, water and heat. Owing to the difficulty of ascertaining whether clothes have been properly heated during the washing processes, and the possibility of the transmission of infection when not properly heated, all clothes washed in steam laundries should be dried upon the premises. The absence in the average steam laundry of proper sorting rooms for the clean linen and the consequent contact with soiled linen may result in a possible reinfection of the clean clothes.

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ORIGINAL ARTICLES

THE ETIOLOGY OF SPRUE.

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THE object of this paper is to demonstrate that the species of Monilia first described by me in March, 1915[1] is the determining etiological factor in sprue, and to suggest that this species be recognized as Monilia psilosis, Ashford, 1914.

It was stated in a paper presented by the writer May 13, 1915, before the annual meeting of the Association of American Physicians,[2] that Dr. Isaac Gonzalez, member of the Institute of Tropical Medicine and Hygiene of Porto Rico, working with an antigen prepared from three strains of this species furnished him by me, had demonstrated in 4 cases of sprue a deviation of the complement, and that in 12 cases not sprue no such deviation could be obtained. The consensus of opinion expressed individually after that meeting was that until the demonstration of a reaction specific to this particular organism should be forthcoming the results should be considered to be due to a group reaction, thus withholding the decision as to the relation of my organism to sprue, although all other evidence, clinical, epidemiological, and mycological, as well as animal experimentation, spoke strongly for its specificity.

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[1] A Monilia Found in Certain Cases of Sprue, Preliminary Note, Jour. Am. Med. Assn., March 6, 1915, lxiv, 810–811.

[2] Studies in Moniliasis of the Digestive Tract in Porto Rico, AM. JOUR. MED. SC., 1915, No. 5, cl, 680.

For the solution of this problem, after six months' more preliminary work, I determined to make a study of a series of 100 persons, some of whom were clinically free from sprue, some typical cases of the disease, and some whose clinical picture did not permit of a positive diagnosis, considering, however, as sprue only such cases as should prove themselves positive, clinically, mycologically, and serologically. Only very slight and justifiable departures have been made from this plan, as will be seen later.

The interpretation of the deviation of the complement, as is well known, is not only a matter into which the personal equation enters, but such highly specialized laboratory work requires long
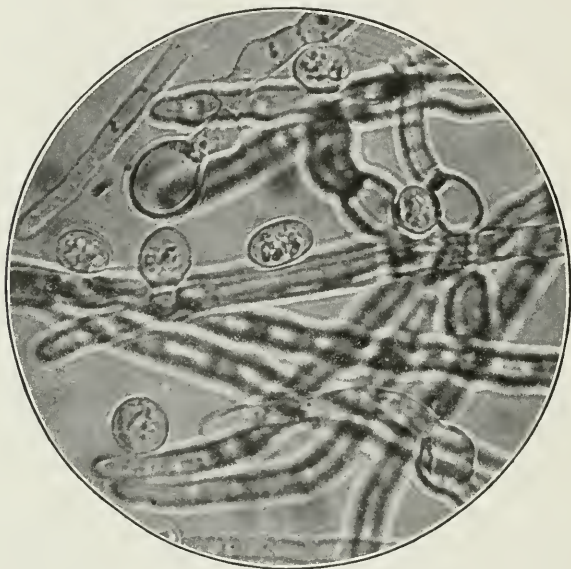
Fig. 1.—Non-specific commensal from a case of pellagra. Case CCXXIa. Note short articles, heavily nucleated and granular yeasts and large size of the elements. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

experience, careful technic, and, in short, genuine ability. It was evident that such reactions should be made by some such person who should have no knowledge whatever of the clinical and mycological history of the case, and who would simply receive the blood of the patient without any inkling of such history, without even seeing the patient. Dr. Gonzalez Martinez, whose previous work has been mentioned above, was on a visit to the North, and the uncertainty of my being able to continue this research without interruption was very great. I was fortunate enough to associate myself in the study of this series with Dr. Carl Michel, of the U. S. Public Health Service, recently assigned to duty for his service in San Juan, and now a collaborator in this institute. This serologist

had spent a long time, previous to his arrival here, in doing this very kind of blood work in syphilis and experimentally in other diseases, and was peculiarly prepared by his experience to fill all of the requisites desired. The results, of course, have been recorded as received from him and incorporated with the clinical and myco-logical history of each case. His own report appears elsewhere in this JOURNAL, and his technic and conclusions are expressed individually.

So while there has been a great effort made to elucidate the facts in this series, there has been no straining after-effect nor any diver-gence from the avowed intention to let these facts speak for themselves.

Fig. 2.—Wild yeast found in feces. Case CLXXVIb². (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

The work has been, as can be imagined, a very arduous one. Not only was it necessary to obtain a clear history in which neither patient nor physician would unconsciously accentuate important symptoms, but a thorough mycological study of the tongue-scrapings and feces was exacted in each case. This latter work was most time-consuming, as plate cultures had to be made of all Monilia-like colonies, and as frequently more than one species was found, and each had to be plated out and run through the proof media, several hundred such cultures were necessary.

With two or three exceptions all of the series were personal cases of the writer, and were seen by him and treated day by day, week by week, thus adding the control of the clinician to the labora-tory findings.

The routine observed was as follows: After the clinical history had been taken, cultures from scrapings of the tongue on glucose agar slants and streak cultures from the feces in glucose-agar plates were made. Suspicious colonies were plated out for pure culture on a 4 per cent. glucose-agar (Sabouraud), + 2 acidity. These plates were incubated for from three to five days. At about the same time a technician of this laboratory, Mr. Jose Loubriel, secured 5 c.c. of blood from a vein of the arm, the blood tube was given a key designation, and it was delivered to Dr. Michel for serological examination after previous centrifugalization and decomplementation. The plate cultures were now examined with a hand

FIG. 3.—Yeasts and hyphæ, Monilia psilosis. Case CCXXXIIIb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

glass and all Monilia-suspicious colonies were fished. This process is an important one and taxes the skill of the operator, as fine differences in color, consistency, and polish of the surface make for success. The selection of the right creamy colony when small is most difficult, and often impossible. Only after repeated plating of feces in quiescent cases of sprue was it possible to demonstrate Monilia psilosis, and in some, as will be seen, they have not yet been isolated, due to the fact that the wrong colony has been fished or that the surface yeast production in the infected intestinal canal is insufficient to give colonies in a limited number of plates. It is well known that in the quiescent stage of sprue, where neither tongue nor intestine is acutely inflamed, only the past history and present

cachexia remain to justify a probable diagnosis. It has been suggested by the writer that in such cases the mycelial elements lie latent in the submucosa awaiting a favorable opportunity to bud and spread yeasts over the surface. In such cases a serological examination will demonstrate a positive reaction, generally weak, and yet only persistent effort will reveal a chance colony. Of course, it is possible that the group reaction, of which I will later speak, is responsible for the serological result, but that this is unlikely is evident from all of the overwhelming evidence presented heretofore, in previous papers, and especially from the fact that time and again repeated work reveals a stray colony of Monilia psilosis after several

Fig. 4.—Young cultures of Monilia psilosis showing typical yeasts before internal structures are characteristic. Case CCXXXIIIb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

failures in a case giving from the first a positive serological result. Cases 10, 42, 62, 77, 97, 98 and 99 are included in this series in order to be perfectly consistent, but I consider them incomplete until future search fails to reveal the organism. Even then the possibility that antibodies remain in the blood after disappearance of Monilia psilosis is to be considered. It should be noted, however, that 4 of these patients were cured two years ago and that their serological reaction is made now for the first time; also, that all save the last 3 have only a weak positive deviation of 25 per cent. or less. When to all of this is added the fact that antigens of other species have been used side by side with an antigen prepared from Monilia psilosis, with generally a negative, rarely a faintly positive

reaction, the group reaction, if present, must be considered of little importance in obscuring a diagnosis when a strongly positive reaction is obtained with Monilia psilosis.

Four or five days should be allowed for the development of Monilia colonies of sufficient size to permit even a guess at the species. Thus about ten days are required to acquire a pure culture. In each case all Monilia-suspicious colonies were planted separately and given a designating letter under the case number, the custom

FIG. 5.—Sabouraud agar slant. Typical culture seven days Monilia psilosis. Case CLIX. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

of examining the cultures previously under the high-power lens being observed in order to avoid sowing bacteria. After two days more the pure culture with its number and designating letter was sown in each of the following media:

Glucose bouillon, 4 per cent., plus 2, in U-fermentation tubes
Levulose   "   "   "   "   "
Maltose   "   "   "   "   "
Saccharose   "   "   "   "   "
Litmus milk
Plain gelatin
Sabouraud agar slants, 4 per cent. glucose, plus 2.

All save the gelatin stabs were incubated at 32 C. As soon as a U-tube showed fermentation the percentage of gas in the blind arm was read and the media was titrated against a sterile control to determine the gain or loss in acidity by the method recommended by the Bacteriological Committee of the American Public Health Association. The special value of this morphological study of cultures sown in each of four distinct sugar media was that one failed to remember, and, by the special method of recording, failed to see what the appreciation had been in the other three, which were
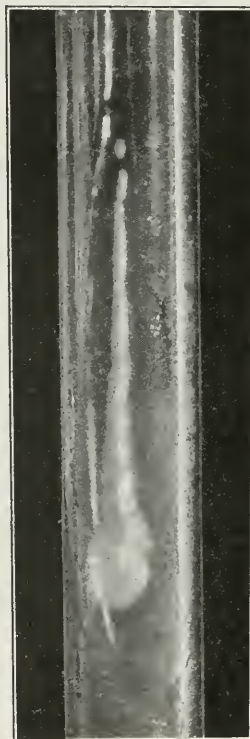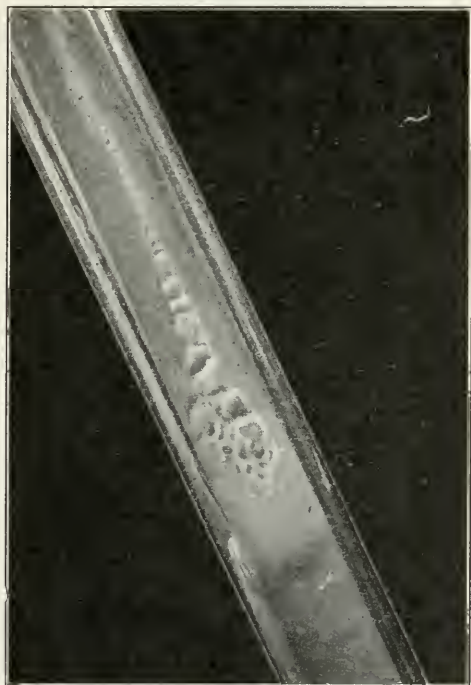

FIG. 6.—Sabouraud agar slant. Old culture Monilia psilosis. Case II. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

generally made along with many others on different days. Hence, when the note "typical" was found under all four media in the final grouping of reactions the check had been made on the personal equation of the mycologist's appreciation of form, etc.

All cultures in U-tubes failing to ferment were allowed to run fourteen days, at which time they were microscopically examined and titrated as above. The reaction in litmus milk was appreciated after fourteen days by comparing the sown tube with a control. An assistant covered the number of the culture with his hand and the color test was made by myself without knowing which was the

control and which the culture. Gelatin stabs were also allowed to
run fourteen days before recording results. The gross appearance
of the growth on Sabouraud agar slants was recorded after seven
days and again in two weeks or more.

Bearing this unvarying technic in mind, let us consider the charac-
teristics of Monilia psilosis:

MONILIA PSILOSIS, ASHFORD, 1914. This organism has been
described by me in the two articles to which I have made reference
at the beginning of this paper, but although no correction need be
made of this original description some amplification must be made
after several thousand more examinations.
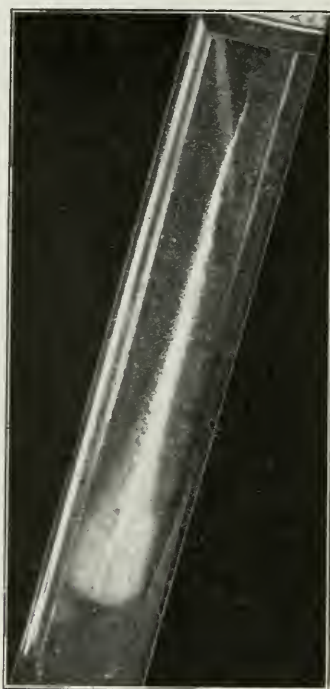
FIG. 7.—Sabouraud agar slant. Aging three weeks Monilia psilosis. Case
CXXIXb. (Photograph made in the Institute of Tropical Medicine and Hygiene
of Porto Rico.)

Morphology. Only after long and careful experience does the
full importance of the morphology of Monilia become impressed
on the mind. For a full year the writer was confused by the varia-
bility of form and size of the elements in even a single mount from a
pure culture. Monilia psilosis is a large, round, bright, clean-cut
yeast, from 4 to 7 micra in diameter, with at most a few granules
and a nucleus. There is also usually a pale vacuole in which a

violently motile bacillus-like body darts about. The contour is always extremely sharp and well-defined, and this contour becomes a shell-like envelope in older yeasts, often thick at one pole, for then the yeast is apt to become oval. This gives it a true signet-ring appearance. The common variations are those of size, multiplication of the nucleus, and increase in the number of the motile bodies, which are then found elsewhere than in the pale vacuole. But it should always be remembered that Monilia psilosis is not typically a granular yeast.


FIG. 8.—Gelatin stab Monilia psilosis. Case LXXVI. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

With this type before us we must be prepared to consider the innumerable variations always present. Reproduction by gemmation throws off great numbers of smaller yeasts, as yet imperfect in development and consequently free from the above-described internal structure, at least as far as an ordinary examination will reveal. In fact, young cultures are apt to show large round yeasts bereft of any such structure. Intermingled with these yeasts are blunt ovals which under the hanging-drop often become hyphæ. It is quite noteworthy that small nuclei and infrequent nucleation are apparently signs of a degraded type, and the patient frequently shows good resistance. Large nuclei and a tendency to mycelial

formation speak for virulent cultures. The degraded and involu-
tion forms furnish the true element of doubt in diagnosis by mor-
phology. A degraded type can be and has been reinvested by me
with all of its morphological characteristics of virulence by passage
through guinea-pigs hypodermically.

If these characteristics be borne in mind the diagnosis of Monilia
psilosis will not be so frequently made and carriers of wild yeasts
or harmless commensals be heralded as carriers of sprue.
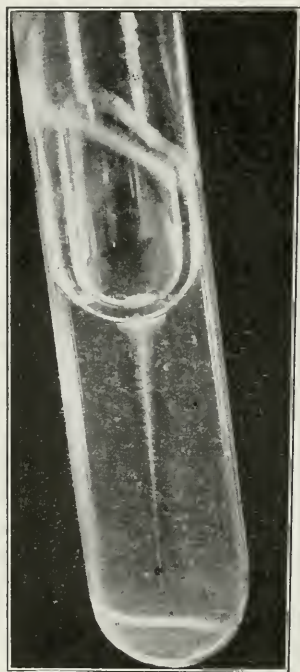
Fig. 9.—Gelatin stab harmless commensal. Case XL. Note short fringe. (Photograph
made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

Monilia psilosis always produces mycelial elements. There are
many strains in which in glucose these elements are not easily
demonstrated, but the crucial test is the gelatin stab. Without the
inverted pine tree in gelatin I have never permitted myself to call
a Monilia, Monilia psilosis. The articles of a hypha are clear-cut,
bright, and not usually very granular. They are of all sizes, 2 to 5
micra wide and of all lengths, sometimes to more than 1000 micra.
They contain pale vacuoles as do the yeasts, but these are molded
to the shape of the article and lie in a line of compartments, giving
the appearance of a bamboo pole sawed lengthwise. In addition,
large and brilliant nuclei are often seen, at times forming a regular
chain of beads from end to end. Budding takes place near the

extremity of the article and offers no peculiarity except that there is never a sterigma, one of the features of sporotrichum. The articles are also usually straight and not knarled, although curious involution forms are at times seen. The extremities of the article are rounded and sometimes bulge slightly. Branching is not frequent. It occurs commonly, but it is not a feature as in some species. There is a decided preponderance in some strains to short single articles otherwise characteristic. Thin structureless, presumably sterile hyphæ, are seen and sometimes granular articles interpolated in a hypha whose articles are for the most part characteristic as described above.
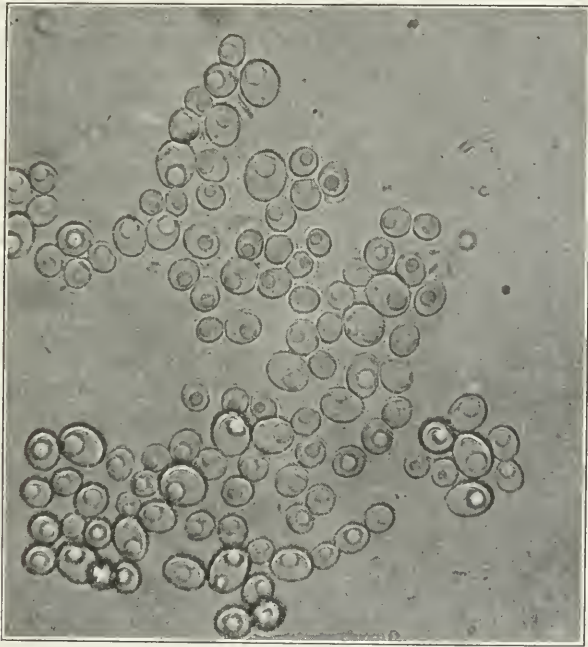
Fig. 10.—Yeasts of Monilia psilosis showing nuclei. Case CXLIXb. (Photograph made in the Institute of Tropical Medicine and Hygiene of Porto Rico.)

That these characteristics are of great aid to diagnosis will be seen in my detailed records, to be later published as a bulletin of the institute, in which at different dates the morphology was described for the same culture in different sugar bouillons. The clear-cut, bright, really beautiful yeast, of large size and globular form, has served to differentiate Monilia psilosis from many other perfectly distinct species. A small yeast $1\frac{1}{2}$ to 3 micra in diameter is not usually Monilia psilosis. A highly granular, highly nucleated yeast should not be ordinarily confused with it. Least of all should a persistently oval yeast. Not that all of these types cannot be found

in a culture of Monilia psilosis, but they cannot be the predominating, the characteristic type.

Litmus Milk. Practically all Monilia I have isolated strike a bluer tone to litmus milk no matter what their species. It cannot be a good proof medium, but it has been religiously employed to exclude Monilia albicans, sensu stricto, Castellani. This fungus I have never yet isolated in Porto Rico, and Bahr's statement that the probable cause of sprue is Monilia albicans I cannot substantiate. In fact, Monilia albicans seems to mean very little culturally and even less morphologically, for no author at my disposal gives a clear mycological differential diagnosis between this organism and the many other species with which it is constantly confused. The only exception is Castellani, and even he neglects its morphology, as, in fact, he does for the most if not all of the species described in his and Chalmers' *Manual of Tropical Medicine.* But Castellani distinctly states that Monilia albicans coagulates and renders litmus milk acid, and that it liquefies gelatin, and these things Monilia psilosis never does.

Gelatin. Monilia psilosis and perhaps other species produce a fine, long, hair-like mycelial extension into the non-liquefied medium. The appearance has been noted as that of an inverted pine tree, and this is fairly descriptive. A Monilia which produces a short, fringe-like, even, close, brush-like extension from the line of the stab is apparently not Monilia psilosis. Much less is a stab which gives off no mycelium. The gelatin stab is a valuable adjunct to a differential diagnosis. The organism of sprue never liquefies gelatin.

Sabouraud Agar, 4 Per Cent. Glucose, Plus 2. The growth on a Sabouraud slant is daily becoming to me of more importance in identifying this species. It is typically a very faint greenish creamy, soft, elevated growth, with clearly defined borders, and, generally, a mycelial extension beneath into the medium. This greenish tinge is by no means easy to define, and the true cream color of commensals must be used to bring it out by comparison. Even more than this, Monilia psilosis itself presents, apparently, at times a true cream color, so that the color alone is not a dependable feature, but when the faint greenish tinge is seen the organism is probably Monilia psilosis, in Porto Rico. The growth, moreover, is shiny, glistening, and brilliant at times. These characteristics are best observed at the end of seven days, as after this the culture changes. Many species were isolated which were waxy, dirty gray, dull, granular, powdery, etc., and none proved to be Monilia psilosis. Some cultures were a brilliant orange, wine-red (Santo Domingo), coral red, or yellow, but all proved to be cryptococci and no mycelium in these vividly colored organisms has been demonstrated. They are not even Monilia. But there are species which must be closely related to Monilia psilosis, and which are difficult to distinguish from it. Especially is this so of a flat, brilliant white,

or cream-colored variety and of a heaped-up creamy growth, both without mycelial extension into the medium.   After a week or so the cultures of Monilia psilosis vary so widely that description fails. A few of the commoner types may be briefed as follows:

1. A dirty cream, with hard, parchment-like covering.
2. A soft, dirty cream.
3. A honeycombed, muddy growth.
4. A heaped-up mass of twisted, root-like convolutions.
5. A pitted, even crater-like, dirty growth.
6. A green, honeycombed growth.

Fermentation Tests.   I take this opportunity of paying a tribute to Dr. Aldo Castellani in his demand that these yeasts be always submitted to tests which will reveal the sugars they are capable of fermenting, at the same time emphasizing again his observation that we do not want to know so much what Monilia can be taught to ferment as to record what they actually do ferment when first isolated; in other words, their usual sugar-fermenting capacity under conditions in which they are found.   Everyone knows what bacteria can be made to do in a changed environment, and if this is true of bacteria it is certainly true of the protein yeast.   But at the same time that I recognize the value of Professor Castellani's proof media, I wish to protest against the creation of species on these fermentation tests alone, even against giving the dominant role to such tests in deciding species.   Morphology is really more important in deciding species, and serological tests even more so, as Castellani himself states, for the latter qualification.

The only sugars normally fermented by Monilia psilosis are glucose, levulose, and maltose (typically, always), saccharose (often), and galactose (occasionally).   I could never accept as Monilia psilosis a yeast which fails to ferment maltose, qualifying this statement, however, by adding that in case of a probably degraded yeast of this species it is permissible to try to restore its full vigor by passage through guinea-pigs.   I have thus reinvested a degraded type on several occasions (case 90 only of this series), with its lost power of mycelial production, its typical morphology, and its ability to ferment maltose; but I have ten times as frequently failed to convert what I imagined must be degraded types into Monilia psilosis, not only by one but by several such passages in particular cultures.   Is it that a degraded Monilia is usually unable to recover its former characteristics, having once lost them, as in the case of the duvet-forming tricophyta; or are we handling separate but nearly related species?   I believe the latter to be the case as cultural departures from Monilia psilosis were rare; their characteristics were generally immutable.

Monilia psilosis follows the universal rule of all Monilia and Cryptococci found here; there is no clouding of the medium when liquid.   A more or less abundant sediment collects, but save when very freshly inoculated, or when gas bubbles up from the bottom

and disturbs this sediment, the medium is clear. This organism rarely produces a pellicle. A collar it does often produce at the point of contact of the surface of the liquid with the glass tube. Gas usually forms in a few days and rapidly increases. The most rapid gas producer is glucose, then levulose, then maltose, except when saccharose is fermented, in which case this sugar yields gas even more quickly than glucose. If gas is produced after seven days it usually, although by no means always, means contamination. All of these sugar media mentioned become more acid after inoculation, as evidenced by titration with phenolphthalein and a $\frac{20}{N}$ sodium hydrate solution against a control. They usually gain from plus 1.5 to plus 5 acidity, but rarely go higher.

These are therefore the routine methods by which Monilia psilosis has been distinguished in this laboratory. Since November, 1914, to date, February 16, 1917, nearly 300 persons, most of whom were suffering from sprue, have had their tongues and feces searched for Monilia, and these Monilia have been classified by methods above described, involving about 500 pure cultures and 8000 differential cultures, of which, in the case of the sugar media, 5000 were separately examined and their morphological characteristics recorded. All of this work, save the serological tests above noted in the last 100 cases, and the final titration of the media in the same cases, has been performed by myself, and to ensure against error I have thrown every possible doubt upon my own technic, often repeating certain cultures, especially those in maltose, over and over again. As a matter of fact, in practically every culture, the differential cultures were sown twice in succession. For these reasons I feel justified in giving what would be under other circumstances judged an unseemingly decided tone to my own views on the specificity of this organism. But I am demanding mycologically only what I have required of myself before a species could be recorded in this paper as belonging to Monilia psilosis. I hope that after the demonstration of all of these details we may be able to show that such strictness is unnecessary.

It has been by no means easy to find Monilia psilosis save in cases of true sprue with active symptoms. Some of the chronic and mild cases have been and are demanding an almost impossible amount of culture work, persistence and patience. But one thing stands out clearly to all who have gone into this laboratory to study sprue. It is unusual to find Monilia psilosis in a healthy man giving no history of past intestinal disturbance suspicious of sprue, and it is very easy to find it in cases with a sore tongue and diarrhea, in which case a 100 per cent. positive serological reaction for the deviation of the complement will, as a rule, quickly reward the investigator.

SUMMARY OF A STUDY OF ONE HUNDRED PERSONS EXAMINED CLINICALLY, MYCOLOGICALLY AND SEROLOGICALLY FOR SPRUE. Sixty-seven were suffering from or had suffered from clinical sprue,

and one was either a carrier or had mild sprue. Thirty-two were healthy or were suffering from other diseases than sprue.

In 61 of the 68 sprue cases Monilia psilosis was isolated. Of the 7 in which it was not found, 4 had been cured for at least one or two years and gave only a 50 per cent. Wassermann positive for Monilia psilosis. The other 3 were mild chronic cases, one with a + (25 per cent.) Wassermann and the other two with a + reaction. I believe that further culture from the feces of these seven would reveal in some or all Monilia psilosis, but it was desirable for many reasons to publish this study without further delay.

Seventy-one persons gave a positive deviation of the complement with an antigen of Monilia psilosis, all but one of the cases of clinical sprue and 4 not sprue. One of the 4 included as not sprue was a case of pellagra in whom sprue may be fairly suspected as a complication from the history; this case gave a + Wasserman reaction. The others were as follows: one a case of nervous dyspepsia with a negative Wassermann using the antigen as first prepared from case 4 but with a positive, 25 per cent. using an antigen prepared from the alcoholic extract of the same strain; one a case of bacillary enterocolitis with a + Wassermann and Noguchi (2 per cent. and 10 per cent. respectively); and one of a healthy boy with an ulcer of the leg giving a Wassermann negative and a + Noguchi.

These reactions were classified both by a percentage scale and by the familiar plus signs, using four pluses, however, to indicate a complete absence of hemolysis, each plus having a value of 25 per cent. Of the 68 cases of clinical sprue: 8 gave a ∓; 13 a +; 15 a ++; 11 a +++; and 20 a ++++. Only one was negative, a girl treated by me for sprue two years ago, in whom Monilia psilosis was then easily found. At the time of the serological examination just made I failed to find Monilia psilosis in scrapings from the tongue and cultures from the feces, and she was fleshy, had a good color was apparently entirely cured. In this connection it is of interest to classify these cases further with regard to their condition *at the time of the serological test.* As is well recognized, sprue is a chronic disease with acute exacerbations—now of the tongue, now of the intestine, at times of both at once. While many other conditions enter into the degree of the deviation of the complement besides the clinical symptoms (and we should remember that severe, apparently essential anemia may be the dominant clinical note in an otherwise quiescent chronic sprue with a nevertheless strong positive serologic reaction), it seems of importance to see how far the degree of the complement deviation accords with the clinical manifestations.

The cases noted in the following table under the heading "Quiescent" are not to be interpreted in the sense that active symptoms had not been personally verified by me and that the word of the patient had been taken for past symptoms justifying a diagnosis. On the contrary the diagnosis has been made on the conditions at

first found and from the intimate acquaintance of the physician with his patient throughout a long period of time, although, of course, past history has been given due weight in substantiating that diagnosis. "Quiescent" means that at the time of taking the blood the active symptoms and signs, sore tongue, and intestinal disturbance were absent. "Active" means, on the contrary, that these signs and symptoms, one or both, were present. In general therefore it is fair to conclude from an inspection of this table that in proportion to the intensity of the clinical picture so will be the deviation of the complement, with the frequent exceptions inherent in so delicate an appreciation.

DEVIATION OF COMPLEMENT IN SPRUE.

Clinical degree of sprue.	Active.					Quiescent.					Cured.				
	∓	+	++	+++	++++	∓	+	++	+++	++++	∓	+	++	+++	++++
Mild . . .	0	0	0	0	0	5	5	5	2	3	1	1	0	0	0
Moderate . .	0	1	0	2	3	1	0	3	2	2	0	0	2	0	0
Severe . .	0	4	1	4	10	0	1	2	0	0	1	1	2	1	2

Finally, in its relation to the question of group reactions it is well to note that in 40 of the 67 cases positive for Monilia psilosis by the Wassermann technic the serum was tested at the same time against an antigen made from other species. The antigens used were as follows:

1. Antigen, Monilia psilosis, Case IV. This was the case from which the organism was first isolated in 1914 and has always been the type upon which I have checked.

2. Antigen, Monilia psilosis, Case CXXXV, Case 89 of the series.

3. Antigen, Monilia species undertermined, an apparently harmless commensal found a number of times in perfectly healthy persons.

4. Antigen, Cryptococcus species undetermined, orange red in color on solid media and a very frequent and harmless inhabitant of the human intestine in Porto Rico.

5. Antigen, combined species of Monilia, in which all Monilia so far isolated by me in this Island were mixed.

Of 24 reactions of Wassermann type performed with antigens 3 and 4, those with the antigen of Monilia psilosis being positive, 21 were negative. The other three all gave a 100 per cent. positive for Monilia psilosis and a + only for one or the other of the antigens of 3 and 4. Of 16 Wassermann reactions performed with antigen 3 alone, 15 were negative and one with a 100 per cent. positive for Monilia psilosis gave a +.

The Clinical Histories. These have been briefed from a question form identical for each case.

THE AGE.

Years.		Cases.
1 to 9	. . . .	1
10 to 15	. . . .	1
16 to 30	. . . .	26
31 to 50	. . . .	33
Over 50	. . . .	7

It might be deduced from this table that sprue is *par excellence* a disease of the prime of life, but in reality it is not so restricted. On

account of the difficulties attendant upon obtaining sufficient blood for the serological tests in the very young, cases under fifteen years had to be usually omitted. Specific intestinal moniliasis is fully as common among children as adults. A goodly proportion of acute and chronic enterocolitis of children in cities, in a country where practically all milk is boiled, are due to Monilia psilosis.

Sex. Males, 26 cases; females, 42 cases. Whether this proportion will hold good for a larger number is problematical. In Porto Rico, as in most countries, women eat more sweets than men, and their tendency to live their lives within four walls undoubtedly lessens their resistance to the effects of a chronic infectious disease like sprue.

Color. Whites, 55; mulattos, 13. Sprue seems to be a rare disease among negros.

COUNTRY.

Porto Rico	48 cases
United States	10 "
Spain	4 "
Syria	3 "
English Antilles	1 case
Santo Domingo	1 "
Venezuela	1 "

All foreigners give a clear history of having been infected a short while after reaching Porto Rico, with the exception of Dominicans. In Santo Domingo the disease is believed to be prevalent in towns, as seen from many cases outside of this series. That sprue is more prevalent among foreigners is clear, as the proportion to Porto Rican residents is not above 1 to 50 of the population in San Juan, and the type of the disease in the former is apt to be more severe.

ECONOMIC POSITION.

Poor	8 cases
In modest circumstances but able to secure an ample food supply	27 "
Well-to-do	28 "
Wealthy	5 "

Sprue is an urban disease and is much more prevalent among those who are able to live well. Therein it differs from pellagra. Its comparative rarity in the country districts among the poor laborers is seen in the result of a careful survey of 10,140 country people in Utuado in 1914, among whom only 11 cases of complete sprue and 19 doubtful cases were seen. The majority of these 30 cases lived in the town of Utuado and not in the country.

OCCUPATION.

Motorist	1	Mayor Domo Sugar Central	1
Housewife	31	Petty Officer, Federal Service	1
Fruit grower	1	Laborer	2
Sugar planter	2	School girl	2
Merchant	2	Society girl	1
Pedlar	1	Chief Engineer, Sugar Central	1
Servant	2	Policeman	1
School teacher	5	Stateman	1
Convict	1	Supervisor schools	1
Navy Officer	1	Collector rents	1
Sister of Charity	2	Artisan	1
Sergeant, U. S. Army	1	Justice of Court	1
Shop girl	2	No occupation	2

DURATION OF THE DISEASE WHEN EXAMINED.

1 month or less	4 cases
1 to 3 months	0 "
4 to 6 months	6 "
7 months to a year	6 "
2 years	8 "
3 years	4 "
4 years	12 "
6 to 10 years	8 "
11 to 15 years	7 "
Over 15 years	7 "
Not stated	6 "

Prevalence of Sprue in Other Members of the Same Family. In 36 cases other members of the family were at the same time suffering from or had presumably had sprue. Sprue is undoubtedly a communicable disease, much as is tuberculosis, in this sense.

The Onset of Sprue. The investigation of these 68 cases has revealed what few if any works on sprue mention, namely, that the onset is often acute and can be dated from a severe "indigestion," "descomposicion," or other acute and often violently inflammatory condition of some part of the upper intestinal tube. This is borne out by the following notes on the mode of onset in these cases:

As food poisoning	1 case
Acute, as gastro-enteritis	22 cases
Acute gastritis	1 case
Acute stomatitis	4 cases
Acute duodenitis	1 case
Total acute cases	29 cases
Urticaria, nausea, bad taste in mouth	1 case
Lassitude, fever, sore throat	1 "
Anemia	1 "
Gradually, with gaseous indigestion	28 cases
No symptoms	1 case
Total beginning gradually	32 cases
Failed to remember how disease began	7 "

Type of the Disease. It is very evident that what we have been describing as "sprue" from the days of Hillary to date is really the terminal phase of sprue. In the *Am. Jour. Trop. Dis. and Preventive Med.*, July, 1915, vol. iii, No. 1, pp. 32–46, "Is Sprue a Moniliasis of the Digestive Tract?," the writer remarks, in connection with the prevalence of "chronic fermentative indigestion" in Porto Rico:

". . . But many (cases) seem to me to be the début of that disease we call 'sprue,' and what I am rapidly coming to believe is merely the terminal phase of a condition commonly disappearing before reaching serious proportions, in this stage of début, as a rule easily controllable from a dietetic stand-point. . . . If we consider that a proportion of the many cases characterized by the 'chronic fermentative indigestion' described are really mild sprue, then we may believe that the disease is usually benign and tends to spontaneous cure."

That this is borne out by my experience here is beyond question.

Therefore, here we have again another point of resemblance to tuberculosis, a disease once only recognized in its ultimate stage, usually that of cachexia, all the preceding stages being covered by a series of glittering generalities, such as "chronic bronchitis," "bronchopneumonia," "grippe," etc., even to "malaria," diagnoses often prompted by whatever superficial condition the "clinical eye" might light on.

But in this series a strict accountability has been had in clinical appreciation: 50 of the 68 cases were complete sprue, incapable of being mistaken even by the dogmatic for any other disease; 18 were cases of incomplete sprue in which either the typical tongue, the typical stools, or the small liver were missing. That these were true sprue there is no reasonable doubt in my own mind, and I hope that there may be none in those who peruse these histories.

Of the 18 cases of incomplete sprue the tongue was always normal in 8; there was no history of diarrhea in 2; and in 12 the liver appeared normal. This organ was small in the other 56 cases. Cachexia was seen in 40 of the 68 cases; a decided sallow color in 10; in 18 no cachexia nor sallowness was observed.

Although the time is too short in the majority to record results of treatment, to date 24 have been apparently cured; 36 are improved, some notably and rapidly so; 6 are still unimproved; 1 was not treated; 1 has just begun treatment.

The type of the disease is expressed in these cases as follows:

Acute	3 cases
" moderate	1 case
" severe	2 cases
Subacute, mild	1 case
" moderate	1 "
" severe	2 cases
Chronic, mild	15 "
" moderate	12 "
" severe	19 "
" intense	8 "
Larval sprue	1 case
Carrier sprue	1 "
Convalescent from sprue	3 cases

CASES NOT SPRUE.

Cancer of the stomach	1 case
Chlorosis	2 cases
Chronic enterocolitis	3 "
Paralysis agitans	1 case
Rheumatic gout	1 "
Hypertrophy of the heart	1 "
Ulcer of leg	1 "
Tuberculosis of lungs	2 cases
Estivo-autumnal fever	2 "
Pellagra	4 "
Stomatitis, lips	1 case
Syphilis	3 cases
" and alcoholism	1 case
Vitiligo	1 "
Neurasthenia	2 cases
Nervous dyspepsia	1 case
Gonorrhea	1 "

Of these cases, 8 stated that cases of sprue existed in their families, the rest denied the existence therein.

In 7 of the 32 the liver was distinctly small. In 13 only species of Monilia other than Monilia psilosis were isolated and yet the serological test with the antigens of Monilia psilosis were absolutely negative, save in cases 25, 46, 50, and 59, two with + reactions and two with ∓.

As to pellagra and the deficiency theory there has been no confusion with that disease in this series, although the danger of such confusion is not to be overlooked when the skin lesions of pellagra are absent. Before the popular knowledge of the existence of pellagra in the United States, even among American physicians, Dr. W. W. King, Dr. Pedro Gutierrez and myself were conversant with its manifestations and reported, as the Porto Rico Anemia Commission, a case in our series for Uncinariasis in 1904 (Anemia in Porto Rico, Government Printing Office, San Juan, P. R., December, 1904). Since that time we have had ample opportunity to observe that while present here it is by no means a common disease. Practically all of the people of Porto Rico eat beans in plenty, no matter how poor or how rich, and this is one of the first lessons the tourist learns, a fact to which our attention was especially directed by Dr. Michel, who has worked intensely on pellagra in the South of the United States and who is as decided as are we that pellagra is not a common disease in Porto Rico. Meat was a common article of diet among the cases which form the basis of this paper, and I have purposely assured myself that the full 95 per cent. could not be taxed with the charge that vitamines were lacking in their diet. It would have to be some mysterious sort of vitamine if such lack existed. Of course, the writer has not lost sight of the justifiable suspicion in connection with food unbalance in that lack of unidentified vitamines or excess of certain classes of foods may tremendously affect the manifestations of chronic infectious processes initiated and sustained by organisms of comparatively little potency. The epochal work on vitamine deficiency seems to be as yet in its infancy.

The skin manifestations of pellagra were missing and the mental symptoms were not comparable to those of pellagra, save in one case. It is not therefore to be ignored that we of this institute who live our medical life here quite as intensely as our confrères in the North, who are unconversant with our local problems, are willing to be deceived by so gross an error in observation. Quite on the contrary the cases of pellagra are clearly diagnosed in this series, and they are all negative for Monilia psilosis, and all but one (a faint positive) are negative also when submitted to the Wassermann test for sprue. That cases of "pellagra sine pellagra" exist—cases by the way which are violently contested by authorities on pellagra—can only be resolved, I believe, by accepting the etiology of sprue as herein recorded and thus clearing up a question until now unanswered.

A STUDY OF TOXINS AND THE SEROLOGICAL REACTIONS IN SPRUE.

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Ashford having shown the relationship of the Monilia psilosis to clinical sprue the necessity of studies of the biological activities of the Monilia psilosis as differentiated from other Monilia led to the use of various serological tests.

Very little being known about the disease-producing substances of the Monilia, experiments were made to determine the toxic substances of the Monilia and what substance could be used as a suitable constant antigen in the tests.

The Toxins. Cultures of virulent Monilia psilosis which had been isolated from fatal cases of sprue, and which, when inoculated (10 c.c.) into a guinea-pig killed it in forty-eight hours, were used. The culture was made on glucose-bouillon incubated forty-eight hours, then shaken in a machine for four hours, and filtered through a Berkefeld filter. From 2 to 10 c.c. of the filtrate were injected into several guinea-pigs. The animals at no time showed toxic symptoms or signs of infection. The same experiments were repeated with emulsions of cultures grown on solid media, and no symptoms of toxemia or infection appeared, which showed that no soluble toxin was present and that the toxin elaborated by Monilia psilosis is not extracellular. As a control, 5 c.c. of the unfiltered culture was injected into a guinea-pig, killing the animal in fifty-six hours. The Monilia was recovered from the heart, spleen, and liver. These experiments led to the study of the Monilia proteins and endotoxins.

Cultures of the Monilia being very difficult to kill, owing to the thermal death-point, which normally is 75° for ten minutes, and as that temperature is injurious to the antigenic enzymes, autolyzation was used as a means to lower the thermal death-point. Cultures of Monilia psilosis were autolyzed by suspending in distilled water, using one six-day culture to 10 c.c. of water. The emulsion was incubated for four days, after which 0.5 per cent. phenol was added and heated to 58° C. for forty-five minutes. Cultures made of the emulsion showed it to be sterile. The emulsion was filtered through a Berkefeld filter and 10 c.c. injected intraperitoneally into a guinea-pig. Slight toxic symptoms were observed from which the animal recovered within twenty-four hours. Five c.c. of the unfiltered emulsion injected intraperitoneally caused an animal to become severely sick with severe diarrhea and toxic symptoms, the animal losing 20 grams within two days. On the third day the symptoms subsided and the animal recovered.

An emulsion of Monilia psilosis was prepared, autolyzed, and killed, one four days slant culture growth being used for each 10 c.c. of 0.5 per cent. phenol solution. Animal and cultural tests were made to test its toxity and sterility. Fifteen persons, who gave no clinical symptoms of sprue and who in no way had been exposed to the disease, were injected. Each person was injected subcutaneously with 0.15 c.c. of the emulsion. A slight local reaction was noticed at the site of injection, which lasted about eighteen hours and then gradually disappeared, leaving a small indurated area. In one case there was a slight rise in temperature which dropped after forty-eight hours.

Several persons who had typical sprue were each injected with 0.1 c.c. of the emulsion. A pronounced reaction resulted and there was an aggravation of all the sprue symptoms. The reaction lasted for three or four days and slowly subsided. The local reaction persisted for five days. This showed that the Monilia proteins and endotoxins were to be considered as the active toxic substances in sprue, and would be of greatest antigenic value, and that these substances have the power to stimulate the production of antibodies in man.

AGGLUTINATION REACTION. To determine the specificity of the Monilia an agglutination test was used.

Two rows of tubes were set up, each containing 0.1 c.c. of normal salt solution. The serum of a clinically and culturally positive case of sprue was added in dilutions of 1 to 10, 1 to 5, and 1 to 2. To this was added 0.2 c.c. of a strong Monilia psilosis emulsion. In the other row normal serum was used as a control. The tubes were incubated eighteen hours and the results observed. In the tube which contained 1 to 2 dilution of positive serum a flaky precipitate was found upon slight agitation. The tubes containing the normal serum, upon agitation, remained uniform. Using this test as a basis a number of tests were made in which an emulsion of a Cryptococcus and normal serum were used for controls.

It was found that the agglutination test using the Monilia emulsion and known sprue serum was positive in only the cases which had severe sprue, with the serum of mild or latent cases the reaction was negative and no perceptible agglutination resulted.

Precipitin tests using Monilia filtrates were tried and did not yield any satisfactory results.

COMPLEMENT-FIXATION TEST. The complement-fixation test in sprue requires careful interpretation. In order to establish a positive standard, careful preliminary tests were made to determine the specificity of this test to the clinical cases. All of the tests made were checked up clinically and mycologically by Ashford.

PREPARATION OF ANTIGENS. Cultures of Monilia were made on Sabouraud's glucose media, incubated four weeks. The growth was washed off with distilled water, using one culture to 10 c.c.

The emulsion was shaken in a machine for two hours and incubated for four days to allow autolyzation. Half of 1 per cent. phenol was added as a preservative and the emulsion heated to 58° for one hour. Cultures were made as to its sterility. It was then titrated for its hemolytic and anticomplementary action. In the tests 1 c.c. was used as a standard. This emulsion has been used six months and the standard has not changed, which makes it a very stable antigen. Old cultures make the best antigens. Antigens made of young cultures lose their stability. Antigens made from the liver and heart of animals that died of acute sprue were of no value. Liver extracts from a patient dying of sprue gave unsatisfactory results.

ALCOHOLIC ANTIGENS. Emulsions of Monilia made in distilled water and incubated, after which the emulsion was heated to 58° for one hour and shaken in the machine for four hours. The emulsion was centrifuged and the supernating liquid poured off. To 1 c.c. of the sediment 15 c.c. of alcohol were added and incubated for two days. In the tests 1 c.c. of a 5 per cent. solution was used. The antigen showed positive in many cases, but was not constant in the delicate tests. The most preferable antigen is the watery emulsion, which is the most constant. The anticomplementary action of this emulsion is about 0.25 c.c. In the actual tests 0.07 to 1 c.c. was used.

SERUM. Serum used was decomplementized by heating for an hour at 56° C., 2 c.c. of serum used. It is advisable to heat all serum to destroy the thermolabile anticomplementary enzymes. If natural only 1 c.c. was used. It is of interest to note that in Porto Rico the complement content of human blood was extremely high as compared to the United States, and heating at the 56° for thirty-minutes did not destroy all the complement. This was overcome by heating the blood at 56° for an hour and allowing it to stand for at least twelve hours before using.

COMPLEMENT. In these tests 0.3 c.c. of a 10 per cent. solution of guinea-pig serum was used.

AMBOCEPTOR. Antisheep amboceptor $\frac{1}{1000}$ solution of serum titrated so that 1 unit = 2 c.c. In the tests $1\frac{1}{2}$ units or 0.3 c.c. were used.

ERYTHROCYTES. 1 c.c. of a 5 per cent. solution of sheep corpuscles were used.

TECHNIC. The technic employed in these tests were the Wassermann, Noguchi, and a modified Wassermann in which concentrated serums were used.

In the Wassermann test two series of tubes were set up. One series containing 0.1 c.c. of normal serum. In the other 0.2 c.c. of inactivated serum was used; 0.7 c.c. of Monilia psilosis antigen was added to each series. A control series of five tubes each was set

up for each test, and the following antigens used; 0.1 c.c. of antigen prepared from a non-virulent Monilia isolated from feces, 0.1 c.c. of a white Monilia antigen, 0.1 c.c. of a red Cryptococcus antigen which was isolated from feces, 0.1 c.c. of a combined antigen prepared from mixture of all the antigens used. Another series of controls using syphilitic antigen was used. To all these tubes 0.3 c.c. of a 10 per cent. guinea-pig serum was added and 1 c.c. of salt solution. The tubes were then heated in a water-bath for half an hour, after which 0.3 c.c. of $\frac{1}{1000}$ antisheep amboceptor and 1 c.c. of 5 per cent. sheep erythrocytes was added. The tubes were again incubated for thirty minutes and the results taken.

In the Noguchi test similar technic was employed, using the same number of controls.

In the modified Wassermann test 1 drop of serum, 2 drops of antigen, 1 drop of undiluted complement and 10 drops of salt solution was placed in each tube. The tubes were then incubated for twenty minutes at 37° C., after which 2 drops of $\frac{1}{1000}$ sheep amboceptor and 0.2 c.c. of 10 per cent. sheep corpuscles were added. The tubes were again incubated for half an hour and the results taken. The Noguchi method proved to be the most delicate, and when this test was negative the cases were also found to be negative mycologically and clinically. In all cases which gave a positive result by the Wassermann reaction the Monilia psilosis was isolated from the feces and the case had clinical symptoms, with the exception of a few described in Ashford's article. The results of all these tests depend upon having proper antigens, and it is noted that antigens prepared from young cultures will not give a pronounced reaction.

SPECIFICITY OF THE TEST. Out of over 400 tests made, including various diseases, all cases which were diagnosed clinical sprue and from which the Monilia psilosis was isolated from the tongue and feces, the complement-fixation test was positive.

The other Monilia antigens used have faintly positive results only in severe cases of sprue. In these tests the results with other Monilia antigen was about 15 per cent. positive, while the reaction with the psilosis antigen was 100 per cent. positive. It is of interest to note that this reaction varies with the condition of the patient. In cases of chronic or latent sprue, and in cases which had recovered, the reaction tends to become negative.

Guinea-pigs which had been injected twice in ten days with 5 c.c. of a non-virulent Monilia psilosis culture gave positive tests, and as the animal recovered the reaction became negative.

Cases which had clinical syphilis and sprue, the fixation test for both these diseases was positive.

Pellagra having been demonstrated by Goldberger as a diet deficiency disease, the same view has been taken regarding sprue. In these series several cases of pellagra were included. All these

cases were severe and had typical symptoms of that disease, and in no case was the Monilia psilosis isolated. The complement-fixation test in all these cases was negative, with the exception of one faintly positive.

Guinea-pig serum of an animal which had been inoculated with a killed culture of Monilia psilosis gave a strong positive reaction.

It is of interest to note that the serum from animals which had been inoculated with live cultures or killed cultures of Monilia psilosis gave the same results as the serum of patients that have sprue, and from which the Monilia psilosis had been isolated from tongue and feces. In view of these results and with Ashford's clinical and mycological work it is strongly evident that the Monilia psilosis of Ashford is the etiological factor in sprue. At the present time tests are being made daily in this laboratory, with the same constant results as described in this article.

THE DISINFECTION OF DRINKING WATER.

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The sterilization of contaminated drinking water is a problem of special importance in war time. The use of bleaching powder, or similar hypochlorite or chlorin preparation, has been used with the greatest success for the sterilization of relatively large volumes of water. The use of water carts containing water treated with a carefully regulated quantity of bleaching powder has given every satisfaction when the method could be satisfactorily carried out, as, for example, when troops are practically stationary. The problem of sterilizing small individual quantities of water, such as are needed by cavalry or rapidly moving troops, is a much more difficult problem which, up to the present, has not been perfectly solved. The use of hypochlorites for such purposes is difficult, owing to the instability of small tablets containing the minute quantity of active disinfectant. In their place, acid sulphates of the alkali metals have been extensively used in tablet form, but the superior potency of many chlorin compounds would indicate that a stable potable chlorin disinfectant suitable for the sterilization of small quantities of water was desirable. With this end in view we have made a number of experiments with various types of substances, one of which we believe to be worth practical application.

TABLE I.—EXPERIMENTS WITH P—SULPHONDICHLORAMINOBENZOIC ACID IN TABLET FORM.

No.	Water treated.	Concentration of disinfectant.	Time of action, min.	Surviving organisms, per c.c.	Tablet dissolved, min.
1	Croton water + B. coli	..	..	63,800	
		1 to 200,000	30	0	4
2	Croton water + B. coli	..	..	38,629	
		1 to 200,000	30	0	9
3	Croton water + B. coli	..	..	112,525	
		1 to 200,000	15	0	9
4	Croton water + B. coli	..	..	112,525	
		1 to 250,000	15	0	9
5	Croton water + B. coli	..	..	112,525	
		1 to 400,000	15	0	10
6	Croton water + B. coli	..	..	178,528	
		1 to 500,000	15	987	10
		1 to 500,000	30	0	10
7	Croton water + B. coli	..	..	125,420	
		1 to 500,000	15	406	12
		1 to 500,000	30	0	12
8	Croton water + 5 per cent. sewage + B. coli	..	..	1,119,000	
		1 to 175,000	15	6,000	9
			30	0	9
			60	0	9
9	Croton water + 5 per cent. sewage + B. coli	..	..	1,158,500	
		1 to 330,000	15	120,064	
		1 to 330,000	30	9,146	7
		1 to 330,000	60	0	7
10	Croton water + 5 per cent. sewage + B. coli	..	..	1,120,000	
		1 to 500,000	15	284,800	5
		1 to 500,000	30	49,318	5
		1 to 500,000	60	70	5
11	Deep yellow polluted river water, B. coli	0	..	33,152	13
		1 to 250,000	20	10,940	
		1 to 250,000	40	852	
		1 to 250,000	60	0	
12	Croton water, B. typhosus	0	..	155,400	
		1 to 225,000	20	0	17
13	Hard water + B. typhosus	0	..	85,400	
		1 to 333,333	20	0	14
14	Croton water, 5 per cent. sewage + B. typhosus	0	..	66,017	
		1 to 333,333	20	242	14
		1 to 333,333	40	0	
15	Croton water, 5 per cent. sewage + B. typhosus	0	..	240,000	
		1 to 225,000	20	13	14
		1 to 225,000	40	0	
16	Croton water, B. paratyphosus A	0	..	112,000	
		1 to 225,000	20	0	17
17	Croton water, 5 per cent. sewage, B. paratyphosus A	0	..	138,000	
		1 to 225,000	20	0	13
18	Croton water, 5 per cent. sewage, B. paratyphosus A	0	..	29,400	
		1 to 333,333	20	15	12
		1 to 333,333	40	0	
19	Croton water, B. paratyphosus B	0	..	322,500	
		1 to 225,000	20	10	17
		1 to 225,000	40	0	
20	Croton water, 5 per cent. sewage, B. paratyphosus B	0	..	309,120	
		1 to 225,000	20	305	13
		1 to 225,000	40	0	

TABLE I.—EXPERIMENTS WITH P–SULPHONDICHLORAMINOBENZOIC
ACID IN TABLET FORM.—*Continued.*

No.	Water treated.	Concentration of disinfectant.	Time of action, min.	Surviving organisms, per c.c.	Tablet dissolved, min.
21	Croton water, 5 per cent. sewage, B. paratyphosus B	0	..	139,776	
		1 to 333,333	20	290	12
		1 to 333,333	40	0	
22	Croton water + V. choleræ	0	..	13,706	
		1 to 400,000	20	0	$12\frac{1}{2}$
23	Croton water, 5 per cent. sewage, V. choleræ	0	..	11,170	13
		1 to 333,333	20	0	
24	Croton water, B. dysenteriæ (Flexner)	0	..	66,998	
		1 to 450,000	15	25	13
		1 to 450,000	30	0	
25	Croton water, B. dysenteriæ (Flexner)	0	..	98,990	
		1 to 333,333	20	17,363	7
		1 to 333,333	40	58	
26	Croton water, 5 per cent. sewage, B. dysenteriæ (Flexner)	0	..	164,864	
		1 to 333,333	20	38	13
		1 to 333,333	40	0	
27	Croton water, B. dysenteriæ (Shiga)	0	..	33,852	
		1 to 450,000	15	12,227	6
		1 to 450,000	30	1,080	
28	Croton water, B. dysenteriæ (Shiga)	0	..	31,200	
		1 to 333,333	20	10,934	11
		1 to 333,333	40	0	
29	Croton water, 5 per cent. sewage, B. dysenteriæ (Shiga)	0	..	2,108	
		1 to 333,333	20	0	13

Our first experiments were made with chloramin-T,[1] but it was
found that when this substance was added to heavily contaminated
waters it required a relatively high concentration to sterilize the
water promptly, particularly in the case of hard alkalin waters.
For example, 1 part of chloramin-T to 25,000 parts of water may
be necessary, and such an amount is decidedly unpalatable. Sub-
sequently, it was found that much lower concentrations of chlora-
min-T were effective if the contaminated water was slightly acidified
with any acid, *e. g.*, citric, tartaric, acetic, etc. Under these condi-
tions, 1 to 250,000 or less of chloramin-T was effective (see Table
III), and the resulting water was not unpleasant to the taste.
But chloramin-T could not be made up in a tablet with the addition
of an acid without decomposition, and the two-tablet system was
regarded as impracticable.

Subsequently, we experimented with preformed toluenesulphon-
dichloramins, since a substance of this type is formed on adding
acid to chloramin-T. The early results were most encouraging
(see Table II), and it was not until we had the product put up in
tablet form that we found it to be unsuitable. The difficulties were
twofold: (1) When the small necessary quantity of dichloramin

[1] The abbreviated name for sodium toluene-p-sulphochloramide. Cf. British Med.
Jour., January 29, 1916. Proc. Roy. Soc., B., 1916, lxxxix, 232.

(0.002 gm. for 0.5 liter of water) was mixed with what were assumed to be inert salts, *e. g.*, sodium chloride, for making into small tablets the very slow normal rate of decomposition of the dichloramin was greatly accelerated. (2) The dichloramin, after dispensing in tablet form, became too insoluble to effect prompt sterilization. The substance had therefore to be abandoned and we turned our attention to a search for similarly active compounds which would show greater stability and solubility.

TABLE II.—EXPERIMENTS WITH O— AND P—TOLUENESULPHON-DICHLORAMIN IN POWDER AND TABLET FORM.

No.	Water treated.	Concentration of disinfectant.	Time of action, min.	Surviving organisms per c.c.	Form of disinfectant.
1	Croton water + B. coli	..	..	11,520	
		1 to 250,000	7	680	o-, powder.
		1 to 250,000	15	0	
2	Croton water + B. coli	..	..	40,980	
		1 to 250,000	7	20	o, powder.
		1 to 250,000	15	4	o, powder.
		1 to 250,000	30	0	o, powder.
3	Hard water + feces, suspension	..	..	22,080	
		1 to 250,000	7	200	o, powder.
		1 to 250,000	15	0	o, powder.
4	Hard water + 10 per cent. city sewage	..	..	64,000	
		1 to 250,000	7	448	
			15	210	
			30	74	
			60	2	
5	Croton water + 2.5 per cent. city sewage	..	..	6,420	
		1 to 250,000	7	0	o, powder.
6	Croton water + 5 per cent. sewage	..	..	18,300	p, powder.
		1 to 250,000	7	1,644	
		1 to 250,000	15	455	
		1 to 250,000	30	0	
7	Croton water + 5 per cent. sewage	..	..	18,300	p, powder.
		1 to 500,000	7	11,928	
			15	2,600	
			30	930	
			60	0	
8	Croton water + 5 per cent. sewage	..	..	18,300	
		1 to 1,000,000	7	19,405	p, powder.
		1 to 1,000,000	15	18,920	
		1 to 1,000,000	30	7,024	
		1 to 1,000,000	60	630	
9	Hard water + B. coli	..	..	161,000	
		1 to 200,000	10	166,400	p, tablet.
		1 to 200,000	40	105,288	
		1 to 200,000	60	56,160	

The substance which is the most suitable that we have yet found is p-sulphondichloraminobenzoic acid, $Cl_2N.O_2S.C_6H_4.-COOH$. It is easily prepared from cheap, readily available materials, and appears to be effective and reasonably stable. The presence of the COOH group confers a slightly greater degree of solubility

in water, which is increased by dispensing it with alkaline salts such
as sodium carbonate or bicarbonate, borax or sodium phosphate.
Formulæ for the tablets are appended, together with details of
the preparation of the substance and an estimate of its cost.

TABLE III.—EXPERIMENTS WITH CHLORAMIN–T, WITH AND
WITHOUT ADDITION OF TARTARIC OR CITRIC ACID.

No.	Water treated.	Concentration of disinfectant.	Acid added, gm. per liter.	Time of action, min.	Surviving organisms per c.c.
1	Hard water + B. coli	..	..	..	2,508,800
		1 to 25,000	None	10	35,200
		1 to 25,000	None	30	14,880
2	Hard water + B. coli	..	..	..	1,120,000
		1 to 300,000	0.4	10	180
		I to 300,000	0.4	30	0
3	Hard water + B. coli + 0.1 per cent. feces	..	0.8	..	3,232,000
		1 to 200,000	0.8	10	0
4	Hard water + B. coli	..	0.2	..	520,000
		1 to 250,000	0.2	10	27,200
		1 to 250,000	0.2	30	7,200
		1 to 250,000	0.8	10	130
		1 to 250,000	0.8	30	50
5	Hard water + V. choleræ	..	..	..	744,000
		1 to 250,000	0.8	10	0
		1 to 500,000	0.8	10	0
6	Hard water + B. typhosus	..	..	..	345,000
		1 to 500,000	0.8	10	1,760
		1 to 500,000	0.8	30	0

Since the systematic name of the disinfectant is inconveniently
long for ordinary use we propose to apply the name halazone to
the tablets containing it. This abbreviated name gives some indi-
cation of the character of the compound.

In Table I are given some of our bacteriological results. The
technic employed was that in general use, and requires no special
description. Five to ten standard drops of the treated water were
generally used for plating on agar and counting the surviving
organisms. Suitable controls were invariably carried out.

From the results in Table I it appears that a concentration of 1 to
300,000 is sufficient to sterilize an ordinarily heavily contaminated
water in about thirty minutes. Such a concentration could be
relied upon to remove coli, typhoid, or cholera organisms. Special
experiments showed that the substance in tablet form was efficacious
when acting on water contained in aluminum bottles, although a
very trifling action on the metal may be observed if tablets are
allowed to remain undisturbed in long contact with the metal.
We believe such action to be of no practical moment. The con-
centration of the disinfectant given above is just perceptible to the
taste, especially in warm waters containing little organic matter;
but the water is perfectly palatable.

The point of advantage of the present disinfectant over most hypochlorite preparations is the fact that the active chlorin is less rapidly used up, so that the process of disinfection continues for a longer period.

Preparation of p-Sulphondichloraminobenzoic Acid. The starting-point in the preparation of this substance is p-toluenesulphonamide, a product which is readily obtained by the action of ammonia on p-toluenesulphonic chloride. The latter substance is a very cheap waste product in the manufacture of saccharin, and is available in relatively large quantities. It is now used for the manufacture of chloramin-T.

Toluenesulphonamide is oxidized to p-sulphonamidobenzoic acid, and the latter substance on treatment with chlorin under suitable conditions gives the desired dichloraminoacid. The reaction may be expressed as follows:
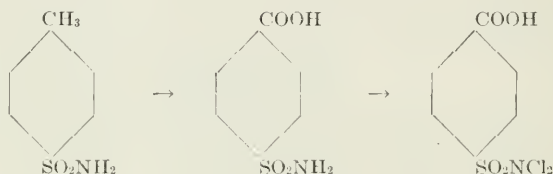
The experimental details are as follows:

Preparation of p-Sulphonamidobenzoic Acid. Add 250 grams commercial sodium dichromate to a mixture of 200 c.c. concentrated sulphuric acid and 600 c.c. water contained in a 2-liter round flask. Then add 100 grams crude toluene-p-sulphonamide and heat on a sand-bath with reflux condenser for one hour, using a small flame at first, as the reaction is vigorous. On cooling, wash the separated crystals well with cold water and then dissolve them in hot dilute sodium hydroxide in slight excess. Filter hot and add excess of hydrochloric acid, and when cold filter off the precipitated acid and wash well with water and dry. The yield is about 80 per cent. of theory. (Cf. Remsen: *Ann.*, 1875, clxxviii, 298.)

Preparation of p-Sulphondichloraminobenzoic Acid. Twenty grams of p-sulphonamidobenzoic acid are dissolved in 200 c.c. approximately normal sodium hydroxide (2 molecules), warming if necessary. About 200 grams of crushed ice is then added and the mixture saturated with a rapid current of chlorin. The reaction is most conveniently carried out in a fairly wide-mouthed flask, which may be shaken while the gas is being introduced. If the temperature should rise materially more ice can be added. A white, rather chalky precipitate of the dichloraminoacid is at once precipitated. The acid is filtered off, using suction, well washed with cold water, and dried *in vacuo* on a porous plate. The dry substance is practically pure, and may be powdered and preserved

apparently indefinitely. Prepared by this method the yield of the dichloraminoacid is practically the theoretical amount (26.86 grams).

The substance is sparingly soluble in water and in chloroform and insoluble in petroleum. It readily dissolves in glacial acetic acid, crystallizing in stout prisms, which melt at 213° C. The substance explodes feebly when rapidly heated on platinum foil, but, compared with most members of the group, is remarkably stable.

The purity of the compound may be checked by titration as follows: 0.1 gm. is weighed out, dissolved in glacial acetic acid and potassium iodide added. The liberated iodin is titrated with decinormal sodium thiosulphate, of which 14.8 to 14.9 c.c. will be required.

The dichloraminoacid dissolves, apparently without change, in excess of cold sodium hydrate solution, and may be reprecipitated on addition of acids. With smaller quantities of sodium hydroxide or with feebly alkaline salts, such as phosphates or borates, hydrolysis occurs with liberation of disagreeably smelling compounds of nitrogen and chlorin.

Preparation of Tablets. We have observed no very marked differences in the behavior of the sulphondichloraminobenzoic acid when made into a tablet with salt and either sodium carbonate or bicarbonate, dry or crystallized borax, or sodium phosphate, although the crystallized or hygroscopic salts are undesirable if the tablets are exposed to high temperatures. The sodium carbonate or dry borax tablets seem as satisfactory as any, and a convenient formula for tablets weighing 100 to 105 mg. is to use sulphondichloraminobenzoic acid 4 per cent. dry, sodium carbonate 4 per cent. (or dried borax 10 per cent), sodium chloride (pure) 92 per cent. The acid should be ground up with the dry salt and the sodium bicarbonate added subsequently. The mixture may be passed through a 40-mesh sieve. No lubricant or other addition is necessary, and should be avoided. The strength of the tablets should be tested by dissolving in acetic acid and potassium iodide solution and titrating with sodium thiosulphate as already described (1 c.c. $\frac{N}{10}$ thiosulphate = 0.00675 gm. of the dichloramino acid). They must not be allowed to dissolve in water and subsequently titrated, as then decomposition occurs. The tablets should be stored in small amber glass bottles.

Tablets so prepared, of the weight mentioned, contain about 4 mg. of the disinfectant, and are suitable for the sterilization of 1 liter or 1 quart of reasonably heavily contaminated water. In the case of extreme contamination a second tablet may be necessary.

Stability of Tablets. The practical success of the disinfectant we propose will depend very largely on the stability of the tablet. At present, sufficient time has not elapsed for entirely convincing

experiments, but it appears, as judged by a very few months' observation, that the stability of the tablets is great enough so as not to destroy their practical value. They are certainly more stable than other similar compounds with which we are acquainted. When kept in amber bottles under ordinary conditions no decomposition was noted in two months. When exposed to bright sunlight, in clear glass tubes, decomposition was more marked, and the same was true of the crystalized borax tablet at a temperature of 38° C. The dried borax and sodium carbonate preparations were stable under these conditions, the bicarbonate ones less so. On the whole the dry borax or dry sodium carbonate tablets appear preferable.

Cost. It is rather difficult to give precise estimates of the cost of the finished product, but it could doubtless be supplied at such a figure that 100 gallons of water could be sterilized at a cost of two cents; the cost of manufacture should not greatly exceed that of chloramin-T, which is manufactured and sold retail at $3 per pound in England and about $4 per pound in the United States. At this figure the cost of the disinfectant for 1,000,000 pints of water would be in the neighborhood of $12 to $16. No allowance is made in this calculation for the cost of tablet manufacture, but this would be a small item.

CONCERNING THE INDICATIONS FOR AND DANGERS OF TONSILLECTOMY.

By George B. Wood, M.D.,

PHILADELPHIA.

The operation of tonsillectomy has become a well-recognized and perfectly justifiable procedure; indeed, it is now one of the most, if not the most, frequently done surgical operation. Not only does it constitute the bulk of the operative work of the nose and throat specialist, but large numbers of tonsils are removed by surgeons and general practitioners. It is true that in a great many cases the operation is easy, presents no special difficulty, and is not followed by any serious disturbances. Yet, on the other hand, it is not free from danger by any means, and even death, as a direct result of the operation, is entirely possible, and in fact many such deaths have occurred. We must admit, however, that the percentage of fatal results is exceedingly small when we consider the enormous number of these operations that are done throughout the country. Other more or less serious complications are more frequent, so that while the benefit that frequently accrues from the removal of an infecting tonsil distinctly outweighs the risk of the operation, it is essential to have a clear understanding of the indications and dangers before submitting any patient to this risk.

Theoretically, the indications for the removal of the faucial tonsils may be divided into two classes: (1) those in which the tonsils are responsible for local disturbances, and (2) those in which the tonsils act as a gateway of entrance for a systemic infection. Usually, however, a tonsil which produces local disturbances also affects the constitution more or less gravely, although the converse of this does not hold as many small unimportant looking tonsils, locally benign, are the seat of hidden but serious focal lesions.

It is seldom that the indications for the removal of the tonsils are so absolute as to demand immediate intervention, yet it is conceivable that an acute inflammation of unusually large tonsils may bring about serious interference with respiration. It is advisable, under these circumstances, to remove one or both of the tonsils rather than to do a tracheotomy.

Patients suffering from repeated attacks of suppurative tonsillitis (the so-called follicular disease), or those who have recently had one or more attacks of peritonsillar abscess, should undoubtedly have their tonsils removed. If any of the tonsillar attacks are followed by infectious processes in other portions of the body, localized or general, surgical interference becomes all the more imperative. Yet we must remember that patients who have recurrent tonsillitis usually but not always have their attacks at fairly frequent intervals for a period of about ten years. Then either because the patient has established some form of immunity against these attacks, or for some peculiar change in the tonsil itself, the attacks become less severe, less frequent, and gradually cease. No matter at what time of life the attacks begin, there seems to be the same cycle of years of repeated attacks, and at the end a cessation of the disease. This biological fact is very important when it comes to the advisability of operative interference.

Tonsillar enlargement is not necessarily an indication for operation unless the extent of hypertrophy is extreme, giving rise to obstructive symptoms. Yet a greatly enlarged tonsil is more frequently the sourse of systemic infection, and, on the whole, is more apt to be repeatedly inflamed than the smaller one. When the enlargement of the tonsils extends upward and outward into the palate the upper surface of the palate may be raised so as to distinctly interfere with Eustachian drainage, a condition which predisposes to otitic disturbances. Also, it must be remembered that embedded tonsils may reach an enormous size and still appear comparatively insignificant under casual inspection.

When patients are to be subjected to etherization for the removal of an enlarged pharyngeal tonsil (adenoids) it is best at the same time to remove the faucial tonsils if there is the slightest indication of trouble originating from them, except when that trouble is insignificant and there is a distinct reason for avoiding any more surgery than necessary or in children under two years of age.

The occurrence of large masses of accumulated debris in the tonsillar crypts often calls for tonsillectomy, but this condition is frequently found in normal healthy individuals with the production of little or no distress except perhaps for a slight local discomfort. Sometimes these cases can be kept under control by appropriate local treatment, but a cure is seldom accomplished without some form of operative interference.

The most difficult type of cases in which to advise patients wisely is those in which there is reason to suspect that the tonsils may be responsible for some cryptogenic toxemia.

First of all we must recognize that the tonsil is not the sole source for the absorption of infectious material, and that unless specific conditions exist as to the etiological importance of the tonsil, these other sources must be sought for and eliminated before judgment is passed. If there is a history of arthritis or other constitutional disturbance following directly upon tonsillar inflammation, and the crypts of the tonsils contain large quantities of cheesy debris, with enlargement of the tonsillar lymph nodes, the responsibility of the tonsils would be practically established. Yet there exist other cases of systemic intoxication in which the infection has come through the tonsils and in which neither by the history nor by direct inspection can any tonsillar abnormality be found. Between these two extreme classes of cases are many others in which by careful study not only of the local appearances of the tonsils but also of the history of the case one may find important connecting data. It must be admitted, however, that the decision to operate often is determined by excluding other sources of infection. Considerable help can often be had by taking cultures from the crypts of the tonsil, but this must be done carefully. A simple technic follows: anesthetize with a 10 per cent. solution of cocain and after a five-minute interval apply tincture of iodin to the surface of the tonsil. The tongue should be held firmly depressed and the patient urged not to gag or to swallow. A small sterile firmly wrapped cotton applicator is passed into the mouth of the crypt through the iodinized surface, an effort being made to obtain material from the bottom of the crypt. As soon as this has been placed back in the tube, and before the patient has swallowed or gagged, a second sterile applicator should touch the surface of the tonsil in the region of the crypt for a control inoculation. Cultures made in this way frequently show pathogenic organisms in pure growth. Sometimes these organisms when tested with the patient's blood will give some biological reaction indicative of their etiological importance to the systemic condition.

When, in spite of the most careful studies, there still exists a doubt as to the role played by the tonsils the decision for or against operating should depend upon the severity of the general condition. In cases of arthritis deformans, of recurrent attacks of acute

rheumatoid arthritis, or some equally severe general infection, if any suspicion, no matter how small, can be placed upon the tonsils the patient should be given the benefit of the doubt and complete enucleation carried out. It is the severity of the general condition that warrants our interference and placing the patient under a certain amount of surgical risk. It is absolutely essential that the specialists work in association with the general practitioner in determining the advisability of the tonsil operation in these cases.

THE DANGERS OF TONSILLECTOMY. It is not probable that the absence of the tonsillar tissues in the throat is ever prejudicial to health. Theoretically, the tonsillar tissue is of importance to the child in its early development, that is, before two or three years of age; but personally I have never seen any harm caused by either the removal of the faucial or pharyngeal tonsils except that which is due directly to the operation.

The choice of an anesthetic is important. In children, general narcosis is always advisable, and ether given by the open method is the safest anesthetic to use. The nitrous oxide-ether sequence is advisable in adults, but it is not safe in children. At the time when the nitrous oxide is stopped and the ether begun not only may there be a temporary suspension of respiration, but sometimes marked weakening of the heart action may develop even to a temporary absence of the wrist pulse. It should never be used in children under ten years of age.

The use of chloroform in tonsillar operations is absolutely unjustifiable even when given by a skilled anesthetist. Sudden death directly attributable to the chloroform itself has occurred too frequently to justify its use simply because of its convenience of administration.

Acidosis due to a general anesthetic follows more often after chloroform than after ether, but I have seen one case following a comparatively short and light ether narcosis in which the child was very ill and narrowly escaped death. The symptoms of severe acidosis do not usually begin until twenty-four hours after the operation, and may occur up to three days. Apparently those occurring at a later period are more severe and very apt to be fatal. Belonging to this group are the cases of delayed chloroform poisoning.

A slight degree of acetonuria is not an uncommon condition following ether anesthesia. It is transient and not accompanied by any severe symptoms. Vomiting, however, is usually prolonged and recovery is somewhat delayed. To guard against this, bicarbonate of soda in large doses should be given for twenty-four hours before the operation. The routine use of bicarbonate of soda has given very gratifying results, reducing the vomiting to a minimum and apparently making the postoperative sore throat less painful.

In selected cases local anesthesia in adults by the infiltration method is almost ideal, except that it is difficult to obtain complete

anesthesia, and in individuals with irritable throats it is often impossible to do a satisfactory operation. Also, if there is a severe hemorrhage the bleeding is much more difficult to control and may eventually require general anesthesia.

Possibly the most disagreeable accident of the tonsillar operation is hemorrhage. In the majority of cases of bleeding following tonsillectomy when moderately profuse is venous, and comes from an irregularly disposed group of veins found most frequently just below the tonsil or in the posterior pillar, rarely externally or in the anterior pillar. These veins at times are of considerable size, so that bleeding following their rupture may be quite profuse. Fortunately, this form of bleeding is easily controlled and stops entirely while slight pressure is being made with the gauze sponge. Generally when the gauze is removed the bleeding recurs only slightly and soon ceases, but sometimes the veins are sufficiently large to require either twisting with a hemostat or ligation. If the bleeding-point can be seen after retracting the anterior pillar a hemostat is generally easily applied. Sometimes a loop of catgut can be slipped over the hemostat, and with the two index fingers deep in the throat the vessel may be tied off just as is done in ordinary wounds. This, however, may be exceedingly difficult or practically impossible, and then a suture should be passed through the tissues immediately above the point of the hemostat. The introduction of the suture is most easily accomplished with a short, strong curved needle with a round point. This is held in the needle holder with the point toward the handle. The point is inserted posteriorly to the vessel and hooked forward. When the point reappears it can be easily grasped with a hemostat, and when released from the holder the suture is readily drawn through. When, as sometimes happens, the exact bleeding-point cannot be determined, a gauze sponge should be placed in the wound and held in position by suturing the pillars over it. If the removal of the tonsil has left an uncommonly deep and narrow fossa it may not be necessary to insert the suture because the gauze sponge is held sufficiently firmly in position by the tonsillar pillars. A silk thread should be tied to the sponge and the end secured on the cheek with a piece of adhesive plaster. This insertion of a gauze sponge into the tonsil wound is also a great help during the operation. It can be inserted immediately after the removal of one tonsil and exerts enough pressure to practically leave the field bloodless for the removal of the other one.

Usually the blood supply of the tonsil comes through several small arteries, so that the bleeding from this source is unimportant. If the tonsillar blood supply comes through a single branch the artery will, of course, be fairly large and the hemorrhage profuse and persistent. This vessel is usually found on the external wall just back of the anterior pillar, near the upper pole of the tonsil, in which position, after retraction of the anterior pillar, it can be easily seen

and picked up. Occasionally the dorsalis linguæ gives off a considerable branch to the inferior pole of the tonsil, and if the tonsil is of large size the artery may be severed close to its emergence from the tongue. The control of hemorrhage in this case may become very difficult, especially as it is hard to determine the source of the hemorrhage, the force of the spurting artery throwing the blood upward along the tonsillar fossa, so that it appears to come from the upper pole. If the point can be seen and picked up all is well and good, but usually extensive packing and suturing of the pillars will be required, and the packing must be so placed as to exert pressure on the exact spot on the base of the tongue.

In the healthy individual it is doubtful whether death will ever occur from hemorrhage when the bleeding comes from such vessels as above described, though the patient may become badly depleted. On the other hand it is within the realm of possibility for the large vessels of the neck to be wounded during a tonsillar operation. Of course, when this happens there is present some rare anomalous condition, probably the most frequent being a tortuous condition of the internal carotid. Several such cases have been reported, and I have seen one case in which a large vessel thought to be the internal carotid could be seen pulsating at the bottom of the tonsillar wound. The large bloodvessel which is sometimes seen pulsating in the wall of the pharynx behind the posterior pillar is almost always the internal carotid artery and not the ascending pharyngeal. The facial artery occasionally before it loops downward to pass around the jaw forms an upward loop which comes in very close proximity to the inferior pole of the tonsil, and though no cases have been reported in which the hemorrhage was proved to be coming from the facial, it is conceivable that it might possibly be injured. Of course, hemorrhage in these cases is shockingly profuse and severe, and only extreme coolness on the part of the surgeon will avert a fatal issue.

While quite frequently a mild degree of infection of the tonsillar wound follows the operative attack in this region, it is remarkable that comparatively few severe infections occur; cases of fatal septicemia, however, have been reported. Probably about 10 per cent. of the cases operated upon show a moderate degree of elevation of temperature, for two or three days following the operation, accompanied by increased sore throat, general malaise, and other indications of a mild degree of sepsis. The appearance of the wound in these cases seldom differs from those running a normal temperature, except that the surrounding tissues are somewhat more reddened and there is generally some edema of the uvula.

Somewhat recently there has been reported a number of cases of abscess of the lung following tonsillectomy, but with one or two exceptions all of these cases have occurred in adults. The method of infection of the lung in these cases is somewhat obscure, though it

seems probable that some of the crypts of the tonsils having contained large numbers of bacteria have been so squeezed during the operation as to force their contents into the throat. This infectious material mixing with the blood or mucus may be inspired, infecting either the healthy lung or what is more likely, some previously diseased area, such as an old tuberculous lesion, which because of its low vitality more readily yields to the bacterial invasion.

The membrane which is seen after injury to the mucous membrane of the throat is not evidence of an infectious invasion of living tissue, but simply a superficial necrosis of the traumatized tissues with a certain amount of fibrinous exudate and numerous leukocytes. There are two important reasons why severe infections seldom result after a tonsillar operation: (1) the wound being perfectly open and free there is no chance for retention of germ-laden secretions, and (2) the action of the saliva is decidedly bactericidal and the constant swallowing removes and prevents infectious accumulations. When there has been a removal of a very deeply embedded tonsil, necessitating perhaps considerable dissection up into the soft palate, we occasionally see a retention of infectious matter due to a healing over of the edges of the wound. This condition somewhat resembles quinsy, but can be easily relieved by separating the edges of the pillars.

One of the more serious complications following as a direct result of postoperative infection is involvement of the ear through the Eustachian tubes. When, however, we consider the mass of infectious material which for days bathes the openings of the Eustachain tubes after an adenectomy the percentage of this complication is surprisingly small. However, middle-ear suppuration directly blamable to the operation on the throat does sometimes occur and may lead to mastoid involvement. A temporary congestion of the drum with a considerable amount of earache is more frequent, but usually clears up within a few days without leaving any serious results.

The chief factor in the production of sepsis of the throat following tonsil operations is excessive trauma, and next to this pyorrhea or other septic conditions of the teeth and gums. Of course, if one operates during an attack of acute infection of the upper respiratory tract he runs a distinct risk of infecting the wound; but unless there is some urgent reason one does not operate under such conditions. In one case in which a tonsillotomy was done during an attack of severe suppurative tonsillitis, because the tissues were so swollen that the patient had distinct dyspnea, the wound did just as well as though it had followed a tonsillectomy done during ordinary conditions.

Deformity of the tonsillar pillars and the soft palate not infrequently follow the tonsil operation, and is usually dependent upon faulty technic on the part of the operator. However, in spite of the most careful surgery there will sometimes be a moderate degree of

cicatricial contraction which may temporarily give rise to a slight amount of pulling sensation in the throat and a peculiar tense look of the velum palati. Also, it sometimes happens that after the operation there is apparent ablation of a portion of the posterior pillar, especially in its upper part, where it merges with the soft palate. This I do not believe to be so often the fault of the operator as to the peculiar anatomy of the individual tonsil and its surroundings. Cases of asymmetry of the soft palate even when no operative work has ever been attempted are not so very uncommon.

In spite of many suggestions to the contrary it is very rare for a permanent vocal or other loss of function to occur as the result of a tonsillar operation. Temporary paralysis of the soft palate either due to a stretching of the muscles or to edema and inflammatory infiltration may, of course, give rise to peculiarities of voice for the time being, and may even be so bad as to permit of a certain amount of nasal regurgitation during swallowing; but these are transient conditions.

Accidental removal of a part or the whole of the uvula, while unfortunate, is not as serious as we are sometimes led to believe, unless the wound is sufficiently large to give rise to a considerable amount of cicatricial contraction. There have been some cases reported in which the tonsillar operation has been so unskilfully if not so brutally carried out that the healing of the throat has been followed by adhesions between the soft palate and the posterior pharyngeal wall. These are avoidable accidents.

When we recall that there are such conditions as hemophilia, the lymphatic diathesis, kidney, heart, and lung affections, and that operating on patients suffering from these things may easily result in death, the importance of a careful preoperative examination of the general condition of the patient is apparent. Death following an operation for abscess of the brain, extensive carcinoma, suppurative peritonitis, or any other condition in which the operative procedure is a forlorn hope, while unfortunate and to be regretted, does not necessarily cast upon the surgeon even a shadow of carelessness or incompetency. But to take a child in apparent health and to subject it to a tonsillar operation, and then have to face a fatal issue, is a most deplorable experience. We as medical practitioners must see to it that such a death cannot in any way be associated with a lack of appreciation of such a possibility or a lack of precaution both before, during, and after the operation.

ACHYLIA GASTRICA.

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Achylia gastrica we understand to be a condition which manifests itself clinically by a persistent absence of free as well as combined hydrochloric acid and also by the absence of gastric ferments.

The total acidity after an Ewald test breakfast is below 10 and after a Leube-Riegel test-meal it may reach as high as 20. In other words we are dealing in achylia gastrica with a complete loss of one of the main functions of the stomach—namely, with that of digestive secretions.

Einhorn[1] was the first to name this disease achylia gastrica. He advanced at the same time the theory that the affection is neuropathic, based on his numerous clinical observations that the gastric contents while showing the absence of active secretions failed to show any pathological evidence of gland destruction.

Martius[2] was likewise of the opinion that achylia gastrica is a neuropathic disturbance of gastric secretions, but he considered it to be in the majority of cases of congenital origin. Different authors (Albu[3] and others) upheld Martius by showing that the disease is not so rare in childhood.

Ewald,[4] who called the affection anadeny gastrica, was of the opinion that it is the atrophy of the gastric glands that causes the achylia.

L. Kuttner,[5] a pupil of Ewald, is so firmly of the belief that achylia gastrica is only the result of a complete disappearance of the gastric glands that he goes so far as to assert that achylia gastrica is a progressive stage of gastritis anacida; in fact, he wishes to have the name gastritis anacida replace the term achylia gastrica. He bases his assertions on the postmortem findings by himself and his pupil Lindeman, whose cases were typical of gastritis with disappearance of the digestive glands. Kuttner also states emphatically that the fact that Einhorn and others found no evidences of pathological changes in the stomach contents of diseased mucous membrane or glands is no proof that there is no disease existing. Kuttner rightfully claims there may exist a pathological condition in the mucous

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[1] New York Med. Press, September, 1888; New York Med. Record, June, 1892; New York med. Wchnschr., July, 1892; New York Med. Record, June, 1894; Arch. f. Verdauungski., vol. i, No. 2.

[2] Achylia Gastrica, 1897.   [3] Berl. klin. Wchnschr., 1903, No. 41.

[4] Berl. klin. Wchnschr., 1892, Nos. 26 and 27.

[5] Krauss-Brugsch: Spec. Pat. and Ther. Innerer Krank., 1914, v, pp. 6-14.

membrane without the stomach contents showing any evidence thereof.

The controversial views outlined above, coming as they do from very reliable sources, prove to us that achylia gastrica may really exist under manifold pathological conditions. In order to make clear the exact underlying cause of achylia and its clinical significance a short review of the physiology of gastric secretions and the factors that govern them is essential.

Exact studies of the physiology of gastric secretions have become possible chiefly through the ingenious studies of Pawlow[6] and his pupils, O. Cohnheim,[7] Richet,[8] Bickel,[9] Cannon, Carlson, F. Umber,[10] Pfanndler,[11] H. Strauss[12] and others.

Gastric juice is almost exclusively secreted in the fundus part of the stomach, the chief cells yielding pepsin and the parietal cells HCl. O. Cohnheim showed that these glands possess a nervous mechanism of their own. Direct mechanical or electrical irritation does not excite secretions in the stomach. On the other hand the sight of food, chewing, or smelling does excite gastric secretion, showing that psychical and reflex influences play an important role in bringing about gastric secretions. Such secretions induced by the sight of food is termed by Pawlow psychical juice; if produced by chewing it has been termed by Bickel appetite juice.

When food reaches the stomach four to six minutes elapse before secretions set in, but it meets there a secretion already possessing digestive properties and serving the purpose of chymification. Bickel demonstrated that the products of the earliest part of digestion are partially absorbed, thus stimulating the secretory and motor apparatus of the stomach.

To study gastric juices in man it is customary to give the patient a standard meal to be removed from the stomach after a definite length of time. After an Ewald test breakfast (250 grams weak tea without sugar and 50 grams white bread) Boas gives the approximate acidity figure of 0.07 to 0.2 free acid and a total acidity of 30 to 70 per cent.; after a test meal (150 grams beef, some potatoes, a plate of soup, and bread) free HCl 0.15 to 0.2 and a total acidity 75 to 87 per cent.

Pure gastric juice as obtained from a dog through the well-known experiments of Pawlow and from human beings with gastrostomy and esophagostomy (Richet, Bickel), or such as was obtained from gastrostomy patients (Umber, Carlson, Bickel), shows 0.4 to 0.5 free HCl and 100 to 140 per cent. total acidity.

[6] Die Arbeiten d. Verdauungsdrüsen, Wiesbaden, 98.
[7] Die Physiolog. d. Verdauungski. u. Ernah., Wien, 1908.
[8] Jour. de l'Anat. et Physiol., 1887.
[9] Berl. klin. Wchnschr., 1905, p. 60; München. med. Wchnschr., 1906, x, 1323; Int. Beitr. zur Path. u. Ther. d. Ernah., 1913, lxxv.
[10] Berl. klin. Wchnschr., 1905, No. 3.
[11] Arch. klin. Med., 1900, xv, 255.   [12] Berl. klin. Wchnschr., 1893, p. 398.

In gastrostomized dogs and human beings with gastric fistula it was found that disgust, anger, or fright stop gastric secretions. On the other hand the sight or smell of appetizing food or pleasing influences increase gastric secretions. Bickel found that nicotin retards gastric secretion. H. Strauss demonstrated that fats and Schuele that concentrated salt and cane-sugar solution have a retarding influence on gastric secretion. ·Meat juices, CO_2, alcohol, diluted sodium chloride solutions, and local heat excite gastric secretions. Most of the amara (extr. fluid colombo, extr. fluid condurang., etc.) were found by A. J. Carlson, contrary to previous belief, to retard gastric secretions.

The average quantity of gastric juice secreted in the course of the day has been calculated to amount to 1500 c.c. The acidity values take a definite course by a reflex mechanism, whereby the acidity rises gradually, reaching the highest point at the height of digestion, and gradually declining, reaching the lowest point when the stomach is empty.

Recent studies were made by Rehfuss, Bergheim, and Hawk[13] of gastric secretions by the so-called fractional method. This consists of introducing a thin weighted tube into the stomach based on the principle of the Gross duodenal tube, after an Ewald test breakfast, and aspirating every fifteen minutes, thereby studying the secretory curve. Similar work was carried on by Max Skaller[14] in Bickel's laboratory in Berlin. They found that even in health the secretory curves vary; they accordingly describe three curves:

1. The isosecretory curve, the height of secretion having a total acidity of 60 per cent., maintaining such acidity for from thirty to sixty minutes, after which it gradually declines. After two to two and a half hours there is a complete disappearance of food residue.

2. The hypersecretory type shows a rapid response to stimuli. Aspiration of contents after five minutes may show an already high total acidity. The highest is 100 per cent. with a gradual decline, and although the food has completely disappeared after two to two and a half hours there still is an outpouring of pure gastric juice for a long·time thereafter.

3. The hyposecretory type, wihch is characterized by a slower ascend, a slower response to stimuli, and a high point of from 40 to 50 per cent. total acidity.

Of paramount importance to the physiology of gastric secretions are the numerous experimental studies of A. J. Carlson,[15] on his subject Mr. V., with a complete closure of the esophagus and a gastric fistula. He found, in contradiction to Pawlow, Bickel, and Schuele that the gastric secretions are continuous and only the quantity of the secretion differs according to the time of day and season. In

[13] Jour. Am. Med. Assn., 1914, lxiii, 909; Am. Jour. Med. Sc., 1914, p. 848.
[14] Berl. klin. Wchnschr., 1913.
[15] Am. Jour. Physiol., 1915, xxxvii, 50. Ibid., 1915, xxxviii, 245.

the morning, on a fasting stomach, the quantity is greater than before lunch or dinner, and more in the summer than in winter. He attributes this change in quantity to the tone in the stomach. Be the quantity of secretion whatever it may it always contains pepsin and a varying degree of HCl. This continuous secretion is, according to Carlson, supposed to be due either to the continuous action of the vagus on the secretory glands or to an autodigestion of the gastric juice.

Another important point brought out by Carlson, confirming the work of Pawlow and Boldyreff,[16] is that the acid concentration of gastric secretion is always the same. The higher or lower acidity obtained from a gastric fistula or through the stomach-tube depends, according to Pawlow, on the mucous secretion in the stomach, and according to Boldyreff and Carlson to the regurgitation of intestinal juice.

Gastric juice has a digestive action on proteids, converting them into peptones and polypeploids; according to Ad. Schmidt it also acts on connective tissue. O. Cohnheim says the HCl also prevents bacterial growth in the stomach, fermentation, and decomposition. Finally, HCl regulates the action of the pylorus.[17]

Normal gastric secretions are kept up by the integrity of the gastric glands, the healthy condition of the blood, and the proper control of the nerves. Disturbances in digestive secretion result when any one of these three factors is at fault.

In relation to achylia gastrica it needs no explanation that an atrophy of the secretory glands of the stomach or a marked pathological change of the blood can be a causative factor. The mode by which a purely functional disturbance of the nervous system may cause a lasting achylia, as asserted by Einhorn, needs a short discussion of the nerves directly influencing gastric secretion. This was made possible by the physiological studies of Langley[18] of the vagus-sympaticus system; the pharmacological studies of Meyer and Gottlieb[19] and the clinical observations of Eppinger and Hess[20] on the same system.

It would be out of place here to go into a detailed anatomical description of the vagosympaticus, but a few remarks on the influence of these nerves on gastric secretion are essential in order to understand how a functional disease of the nervous system can be made responsible for achylia gastrica.

It was Langley who showed that all the organs not controlled by the will (stomach, intestines, bloodvessels, ducts of glands) and also certain organs possessed of striated muscle fibers (the heart, the

[16] Quart. Jour. Exp. Physiol., 1914, viii, 1.

[17] v. Mehrinz: XII Kongr. f. inner. Med., 1893, p. 471. Hirsch: Zentralbl. f. klin. Med., 1892, p. 993; 1893, xiv, 73, 377, 601.

[18] Jour. Physiol., 1898, xxiii, 240; 1911–12, xliii, 173.

[19] Experiment. Pharmacol., Vienna, 1912.

[20] Zur Path. d. Veget. Nerven-System, Ztschr. f. klin. Med., lxvii lxviii, 205, 345.

beginning and terminal portions of the alimentary canal, and the generative organs) are under the control of the vagus and sympaticus system. It was also shown and pharmacologically demonstrated by Meyer and Gottlieb that these two systems antagonize each other throughout the greater extent of their course.

In reference to gastric secretions, which concern us here most, it was shown that the vagus excites secretions and the sympaticus inhabits secretions. Atropin, for example, paralyzes the vagus, thereby causing a cessation of gastric secretions; pylocarpin, on the other hand, stimulates the vagus, thereby causing an increase in gastric secretions. Adrenalin stimulates the sympaticus and so inhibits gastric secretions. Eppinger and Hess succeeded in demonstrating in the human being characteristic manifestations indicating functional disturbance in either the vagus or sympaticus, or both. Individuals with an increased tone in the vagus system they termed vagotoniacs, while those with increased tone in the sympaticus are named sympaticotoniacs. They also showed that there exist clinical evidences of an increased vagus action in vagotoniacs (contracted pupils, increased salivation, slow heart, increased gastro-intestinal secretions), and an increased sympathetic stimulation in sympaticotoniacs (dilated pupils, dry mouth, flushed face, and diminished gastric secretions).

Not all symptoms have to be present in order to stamp one as a vagotoniac or sympaticotoniac. There are numerous cases in which certain organs show signs of vagotonia and other organs again signs of sympaticotonia. For example, the heart's action may give the signs of a vagotoniac's slowness, respiratory arrhythmia, while the stomach shows signs of sympaticotonia (diminished or absent secretions).

It was Eppinger and Hess again who showed that individuals with a disturbance in either of the above-named systems only demonstrate the condition after the administration of drugs influencing either system. Pilocarpin even in smallest doses provokes vagus symptoms, while adrenalin in equally small doses provokes sympaticus symptoms.

In achylia gastrica it is plausible to assume that there is an inborn or an acquired sympaticotonia. It is very probable that the same patients who have during middle life achylia gastrica on the basis of sympaticotonia may have had in their earlier years hypersecretions on a vagotonia basis. Einhorn rightfully expressed the view that the finding of atrophy of the gastric glands in a prolonged case of functional achylia gastrica is due to inactivity of the glands (disuse atrophy). Knowing through the proved studies of von Bergman[21] and his pupils, J. Kauffman,[22] and our own observations[23] that the

[21] München. med. Wchnschr., 1913, No. 4, p. 169.
[22] Ztschr. f. klin. Med., 1914.
[23] Arch. Int. Med., March, 1914.

hypersecretion accompanying vagotonia may eventually lead to pathological changes in the gastric mucosa (ulcus ventriculi) it is reasonable to assume that a prolonged sympaticotonia inhibiting gastric secretions would eventually lead to atrophy of the gastric glands.

ETIOLOGY. The above discussion would lead us to divide achylia gastrica from the etiological stand-point into three groups:

1. Achylia gastrica with destruction of gastric glands either on the basis of chronic, progressive gastritis (Kuttner), or carcinoma, linitis plastica, alcoholic gastritis with cirrhosis of the liver (Lockwood).

2. Achylia gastrica accompanying marked secondary and primary anemias. To this group belongs the achylia of primary pernicious anemia; the marked anemias accompanying tape-worm; the lowered acidity and even achylia in syphilis as well as the achylia described in chronic rheumatism, gout, hyperthyroidism, etc.

Gravitz was of the opinion that pernicious anemia is secondary to toxins developing as the result of the gastro-intestinal disturbance, especially when accompanied by achylia gastrica. Sahli is likewise of the opinion that pernicious anemia is secondary to achylia gastrica because in the absence of HCl the iron is not assimilated.

From the clinical observations, we agree with the authors who make the anemia responsible for the achylia and not the achylia responsible for the anemia.

3. Achylia gastrica of a functional nature. To this group belong the great majority of cases in whom there is a demonstrable disturbance of the vagosympaticus system with a predominating sympaticotonia of the gastric secretion.

Disqué[24] pointed out that these patients either present the type of status asthenicus (Stiller) or that of the status apoplecticus. In the status asthenicus one usually meets with the mixed type (vagosympathicotoniac), while in the apoplectic type the sympaticotonia may predominate throughout the entire system. The not infrequent occurrence of achylia during the menopause as well as the achylia in Addison's disease show the relation of the sympathetic disturbance to the absence of gastric secretion.

The achylia gastrica secondary to gall-stones and appendicitis or other intra-abdominal diseases as pointed out by Lockwood[25] are also in most cases based on a sympaticotonia. The disease in one of the intra-abdominal organs only serves as an exciting factor in bringing about the manifestations of sympaticus disturbance. This is also the reason why the removal of the cause improves even the gastric secretions.

The interesting experimental work of Carlson and Keenton[26] showed that the removal of the parathyroids produce achylia which is remedied by the administration of calcium.

[24] Arch. f. Verd., 1914, xx, 366.   [25] Diseases of the Stomach, 1913.
[26] Am. Jour. Phys., 1914, xxxiii, 25.

MORBID ANATOMY.   In the functional type of achylia gastrica the gastric mucosa will in the majority of cases not show any macroscopic or microscopic changes in the gastric mucosa.

Only rarely will moderate atrophic changes of the gastric mucosa and secretory glands be met with secondary to inactivity of the glands (disuse atrophy).   In the organic type of achylia gastrica partial or complete disappearance of the gastric mucosa is seen with the naked eye.   Microscopically various stages of destruction of mucous membrane and glands are seen, such as fatty and cystic degeneration of the glands and atrophy of the mucosa. Cylindrical epithelia frequently assume the shape of goblet cells; rarely the pathological changes are seen to have penetrated the submucosa, muscularis, and serosa.

Age.   The affection is most common after the age of forty. Individual cases in earlier life are reported.   This affection is much more frequent in men than in women.   It is sometimes met with in diabetes, gout, etc., bad teeth are a predisposing factor.

SYMPTOMS.   The symptoms of achylia gastrica either on an organic basis or secondary to marked anemia are treated when discussing differential diagnosis between the functional achylia gastrica and the above-named affections.   Here only the symptoms pertaining to functional achylia gastrica are being considered.

In a fair number of cases the disease gives rise to no symptoms whatsoever.

There is another class of cases in which diarrhea is the only symptom.   Here the stools contain even macroscopically muscle fibers and connective tissue, and are erroneously treated for intestinal disease when in reality the examination of the stomach contents discloses the achylia to be the causative factor for diarrhea, one form of gastrogenic diarrhea.

Another group of cases of achylia have vague gastric disturbances, fulness after meals, nausea, belching, bad taste, and marked dryness in the mouth, etc.

In a small number of cases the symptoms occur periodically with severe epigastric pains, nausea, sometimes even vomiting.   The pains are independent of meals, spreading over the entire upper quadrant of the abdomen and radiating to the back.   Adolph Schmidt has termed such cases achylia dolorosa.   There may be considerable burning in the stomach not relieved by food or bicarbonate of soda.   The tongue is coated and appetite is lost.   It has even been found that erosions with fatal parenchymatous bleeding resulted in late stages of achylia gastrica.   Such bleeding was explained as being due to erosions caused by regurgitated trypsin into the stomach.

O. Gross[27] describes cases of achylia gastrica associated with

[27] München. med. Wchnschr., 1912.

symptoms pointing toward pancreatic disturbance (bulky, fatty stools, containing an increase in fat, muscle fibers, and starch, and a diminution of the pancreatic ferments in the duodenal contents and stools). He has termed such cases achylia pancreatica. This form of achylia is rare. Whether achylia pancreatica is an independent affection, as O. Gross assumes, or is secondary to a long-standing achylia gastrica, is not definitely settled. Be the symptoms what they may it is characteristic of the functional type of achylia gastrica, that there are very marked intermissions of well-being and that the long duration of the disease does not interfere with the general appearance of the patient. A great majority of these cases even increase in weight notwithstanding their complaints.

DIAGNOSIS. This is chiefly based on the examination of the stomach contents and the stools. From the fasting stomach we can neither by expression nor by aspiration obtain any contents. Lavaging such an empty stomach one obtains pure wash-water in the greater number of cases; in a lesser number mucus of normal macroscopic and microscopic appearance is found. In the smallest number of cases evidence of an inflammatory condition of the mucous membrane and destruction of glands is seen, such as increase in cellular elements and atrophic appearance of the glands.

To draw diagnostic conclusions from pieces of mucous membrane obtained by aspiration or lavage of the stomach must be employed with care, because fragments of mucous membrane are present even normally as a result of the trauma caused by the aspiration. In achylia, aspiration more readily causes pieces of mucous membrane to become separated because of the existing vulnerability in the gastric mucosa.

The non-finding of particles of mucous membrane does not exclude a pathological change in the lining of the stomach. Only the constant presence of pieces of mucous membrane in the stomach content, showing microscopically destructive changes indicates a diseased condition of the gastric mucosa. This is, however, the exception in the achylia gastrica described by Einhorn and Martius and is regularly found in that form of achylia which is a progressive stage of gastritis subacida (anadeny gastrica, Ewald) and the achylia resulting from diseases of metabolism and blood.

The stomach contents obtained seven or eight hours after a Bourget-Faber test meal (250 c.c. barley soup, 2 slices of bread, 50 grams chopped meat, and 8 prunes) have, according to Kuttner and Lindeman, shown a residue of prune shells. They conclude from this there is a diminished motility in certain cases. This is, however, a hasty conclusion as to the judgment of motility in achylia because the remnant of pieces of prune shells in achylia are more likely due to the fact that the shells stick to the gastric wall because of the absence of fluid.

The removal of the stomach contents one hour after Ewald's test

breakfast shows the food to be unchanged, just as if it had only been chewed and only a very small quantity of light fluid flows on top. The food mass shows partially to be interwoven with some mucus. At times no food is obtained one hour after Ewald's test breakfast because of the open pylorus. In such cases we must remove the contents three-quarters or even half an hour after the test breakfast. Such stomach contents are usually entirely devoid of odor, contain no free acid and no combined acids. The total acidity is below 10. Important is the absence of ferments. We must, however, not be satisfied with the diagnosis until a Leube-Riegel meal (400 c.c. meat soup, 150 to 200 grams beefsteak, 150 grams mashed potatoes) is taken by the patient and the stomach contents removed between two and a half and three and a half hours (at the height of digestion). If then no free and combined acids, a low total acidity, and absence of ferments are found the diagnosis is certain. An additional aid in diagnosis has been furnished by Rehfuss and his coworkers by the fractional method of examining stomach contents as described above.

In achylia gastrica we accordingly employ the Gross duodenal tube, and introducing it 50 cm. leave it there for hours, aspirating from time to time. The gastric juice obtained throughout the entire procedure fails to show the presence of free or combined acids. If by the fractional method acid is obtained in the course of digestion one deals with a subacidity or gastritis anacida but not the functional achylia.

Jaworski determines the presence of achylia in the following manner: He gives his patient 300 to 400 c.c. of dilute HCl half an hour before the test breakfast. The contents removed three-quarters to an hour later must show no free or combined acid if there is a true achylia. The examination of the stools may frequently show muscle fiber and free connective tissue. This is particularly marked when diarrhea is present, but even in constipation while connective tissue is not so frequent, muscle fibers are found.

When the disease progresses so that the external secretion of the pancreas is likewise disturbed, fat and starch as well as the diminution of trypsin, amylopsin, and steapsin are found in the duodenal contents and the stools. A diagnostic aid is furnished by Schmidt's test-meal, consisting chiefly of 100 grams of chopped beef half rare. Normally, none or but very few shreds of connective tissue are found microscopically in the stool, while in achylia connective tissue is found in abundance. It must be emphasized that a perfectly normal stool without any evidences of disturbed digestion does not exclude the existence of achylia.

The mode of filling and emptying of the stomach in achylia gastrica as in all gastric affections can best be studied by means of the roentgen ray. The filling of such a stomach, as first pointed out by Holzknecht, is slow. One sees the contrast food stop for thirty seconds or one minute below the air bag, and the food dribbles down

to the lower part of the stomach likewise very slowly. This is attributed to the dryness of the stomach wall.

While this explanation sounds plausible it does not completely satisfy our reasoning that the dryness in the stomach alone should account for the slow filling of the cardiac end of the stomach. It appears to us that the slow filling is rather due to the fact that the air bag (magenblase) is much larger in achylia, thereby interfering with the action of the diaphragm, which, according to Cannon, is so important in filling the cardiac end of the stomach with food and furthering it toward the pyloric end.

Peristalsis of the stomach in achylia differs from the normal in the following manner: normally when the first few morsels of food reach the lower pole of the stomach one sees at once a peristaltic wave in the region of the pylorus, sometimes resulting in antrum formation, although but very little or no food at all passes the pylorus. As the stomach fills up completely with food, peristalsis ceases for four or five minutes, when it is again resumed in its normal manner. It begins at a point just opposite the incisura cardiaca running along the greater curvature forming shallow waves. At a point oppsite the incisura angularis the waves deepen finally, forming an antrum. Very small waves are also seen along the lesser curvature.

To recapitulate, we have a period of peristaltic waves in the region of the pylorus corresponding to the gastric secretion met with by the first morsels of food, brought about reflexly by the act of chewing and deglutition. This peristaltic action may be termed the initial period of peristalsis. Then comes the period of filling and strata formation in the stomach when no peristalsis occurs. This may be termed the period of latency. After four to six minutes, corresponding to the time of the real setting in of secretion, the regular course of contraction waves begins.

In achylia gastrica, on the other hand, because of the absence of secretions, the initial peristaltic wave is absolutely missing. The period of latency is unusually prolonged, and when contraction waves begin they are very superficial. We see, therefore, that the roentgen ray observation in relation to peristalsis of the stomach fully confirms the physiological teaching—that peristalsis of the stomach is primarily dependent to a great extent on the secretions. The superficial peristalsis in achylia gastrica is brought about by the mechanical influence of the food.

The emptying of the stomach is unusually rapid in achylia gastrica; because of the absence of the acid reflex, the pylorus is open. This rapid emptying is also present in the great majority of cases in the small intestine, and in a goodly number of cases there is also hypomotility of the colon (achylic diarrhea).

DIFFERENTIAL DIAGNOSIS. The diseases from which achylia gastrica is to be differentiated are: gastritis anacida, syphilis of the stomach, carcinoma ventriculi, and heterochylia (Hemmeter).

From gastritis anacida achylia is differentiated by the absence of

mucus, the complete absence of ferments, and the non-return of acids by food stimulating secretions or by the giving of dilute HCl before meals (Jaworski). Furthermore, the gastritis anacida has mostly a higher total acidity, and constipation is by far more common than in achylia.

To differentiate achylia gastrica from carcinoma is especially difficult in cases in which achylia is associated with epigastric pains or with a severe anemia. Here all clinical methods helping to establish a diagnosis must be resorted to. The important points are: the higher total acidity in carcinoma, the presence of considerable mucus, an increase in free leukocytes; if stagnation is present we find lactic acid and Boas-Oppler bacilli. In cases in which the carcinoma ulcerates we may succeed in finding cancer cells in the washed-out stomach contents. P. Cohnheim found characteristic flagelli in carcinoma. The persistent finding of occult blood in the stool speaks for carcinoma.

The careful laboratory tests, such as that of Wolf-Junghans, the improved method of staining, the Boas-Oppler bacilli, the formol index, and the glycyltryptophan test,[23] have yielded in a high percentage of cases such valuable results in differentiating carcinoma of the stomach from achylia that it is well worth our efforts to carry out these tests with as much exactness as employed by Smithies.

In the Wolf-Junghans test the patient gets at 4 P.M. on the day previous to the examination one ounce of castor oil. At 6 P.M. of the same day a mixed meal is taken and at 7 P.M. 20 seedless raisins. The following morning the gastric contents are aspirated and lavaged in order to determine whether the stomach is really empty; 200 c.c. of water and 60 grams of two-day old white bread is taken by the patient and removed between fifty and sixty minutes later. The contents are filtered through double HCl-washed filter paper, and the filtrate is first treated for albumin within one hour after removal and then in the following manner.

Into six test-tubes, each of a capacity of 20 c.c., we put stomach contents of $1, \frac{1}{2}, \frac{1}{4}, \frac{1}{10}, \frac{1}{20}, \frac{1}{40}$, c.c. respectively. To each tube enough distilled water is added to make a total of 10 c.c. This furnishes us therefore the following dilutions of the stomach contents:

Tube 1 equals $\frac{1}{10}$.
    2   " $\frac{1}{20}$.
    3   " $\frac{1}{40}$.
    4   " $\frac{1}{100}$.
    5   " $\frac{1}{200}$.
    6   " $\frac{1}{400}$.

To each of the tubes we now add 1 c.c. of the following solution:

Phosphotungstic acid	3 c.c.
HCl (concentrated)	10 c.c.
Alcohol (96 per cent.)	200 c.c.
Aqua dest. . . . . ad	2000

[23] F. Smithies: Carcinoma of the Stomach, Smithies and Ochsner, Saunders, 1916.

If the pearly white zone appears also in the fourth tube the case arouses suspicions of cancer; if in the fifth and sixth tubes we call the result positive.

For finding the Boas-Oppler bacilli Smithies employs the so-called colored agar stain for the gastric extracts, which is made as follows: Prepare a 2 per cent. solution of agar in distilled water. While the solution is still hot filter through double HCl-washed filter paper a few times. Then fractionally sterilize and filter for three consecutive days. Pour 5 c.c. of this solution into test-tubes and plug with sterile cotton.

The stains comprise the following: Unna's polychrome methylene blue and fresh Lugol mixture.

The test is performed thus: Liquefy the contents of one of the test-tubes and divide this into two. To each add 15 drops of stain—the methylene blue to one and the Lugol solution to the other. Mix the contents well and place the tubes in a beaker of boiling water. Now make thin smears of the gastric extracts on two separate slides. Fix these. To each of these add one drop of the staining mixture (the Lugol stain to one and the methylene blue to the other) and drop a cover-slip on each of the preparations. Wait one minute (while the preparations are fixing) and examine microscopically. By this method the Boas-Oppler bacilli stain blue and the starch, etc., is stained brown by the Lugol solution.

Glycyl tryptophan test: Prepare 10 test-tubes, each containing 0.5 c.c. glycyl tryptophan. Add to each 5 c.c. of filtered gastric juice. Then make two additional control tubes, one containing 0.5 c.c. glycyl tryptophan and 5 c.c. of normal saline, the other containing only 5 c.c. of normal saline. To each of the twelve tubes add 0.5 c.c. of toluene, invert the tubes several times and incubate for twenty-four hours at 37° C.

Now have ten clean test-tubes ready. Into each tube introduce 2 c.c. of the mixture below the toluene. To each of these add 3 drops of glacial acetic acid (3 per cent.). Shake tubes well. Then allow bromine vapors to flow into each tube until an amber-yellow color appears. Shake the tubes again. Examine by daylight. A rose-pink color indicates a positive reaction.

Formol Index. This test depends on the property of gastric juice from stomach cancers to split peptone into the amino-acids. Hence there is an ereptic enzyme in the stomach contents in this disease. We determine the presence of this enzyme by the amount of amino-acids found (by titration with decinormal sodium hydroxide to phenolphthalein) after treating peptone solution with the suspected gastric contents. The test is performed as follows:

Into a test-tube 20 c.c. of filtered Witte's peptone solution (5 per cent.) and 1 c.c. of filtered gastric juice are introduced. Now three control tubes are prepared, one containing the above plus 10 c.c. of decinormal sodium hydroxide, another containing 20 c.c. of

the peptone plus 10 c.c. of the decinormal sodium hydroxide, and the third containing the 20 c.c. peptone alone.   To each of the four test-tubes 1 to 2 c.c. of toluene is added (to prevent putrefaction) and are incubated for twenty-four hours at 37° C.   Then 10 c.c. of 40 per cent. formaldehyde which has been treated in the following way is added to each.   The formaldehyde is neutralized with sodium hydroxide to 0.5 c.c. of phenolphthalein (0.5 per cent. in a 50 per cent. alcohol solution).

Now titrate each tube immediately and in gastric cancer one finds in the first tube an acidity equivalent to 20 c.c. and above of the alkali, in ulcus carcinomatosus 19.8 c.c., in cancer of the liver 4 c.c., in gastric ulcer 12, and in achylia 14.

The different biological tests to facilitate the diagnosis of carcinoma as well as the increase of pepsin in the urine, while scientifically interesting, have not aided in the diagnosis of carcinoma.   A great aid in the differential diagnosis is furnished by the roentgen ray, and in a very great majority of cases of carcinoma of the stomach it will supply a clue.

Advanced stages of carcinoma of the stomach show such outspoken changes that a description is not here deemed essential.   Only such cases of carcinoma of the stomach will be discussed the structural changes of which are not so marked, and where, unless a very careful roentgenological study is exercised, diagnosis would be impossible. In studying such cases, as in achylia gastrica the mode of filling, peristaltic action, appearance of stomach, and mode of emptying are to be considered.   The roentgen ray characteristics of achylia gastrica have been mentioned above.

In carcinoma even in early stages there is a tendency to atony of the stomach so that the food drops down, distending the stomach like a bag.   If there is even moderate involvement of the pylorus one sees it fill very slowly, being passively distended, as it were, by the food, unlike the normal pylorus which fills in a ball-like manner, showing visible peristalsis.   Peristalsis is persistently absent in that part of the stomach infiltrated by carcinoma, so that the straight, rigid, and transversely stretched-out lesser curvature with absent peristalsis speaks, as well pointed out by Levy-Dorn and Ziegler, for early carcinoma of the lesser curvature.   The rigid, elongated, tube-like pylorus indicates early cancer of the pylorus.

The appearance of the stomach is practically as described above—bag-shaped with absence of peristalsis in the affected areas, and usually a dextra-position with a tendency to the bull-horn shape of the stomach, the pylorus forming persistantly the most depending portion.   The emptying of the stomach due to the open pylorus is hastened, and at no time does one see the contractile action of the pylorus.   Should the carcinoma of the pylorus have reached a size to offer a partial obstruction to the passage of food we find no change in the mode of emptying in the first part of digestion, but a residue is

present six hours after the meal, although the rest of the contrast substance already fills the entire colon down to the rectum.

A form of carcinoma of the stomach that gives the same clinical symptoms as achylia in the absence of palpatory finding occurs in complete scirrhous involvement of the stomach. In such cases the roentgen ray is of inestimable value. It represents an elongated transversely situated tube-like organ lying high in the abdominal cavity, which is seen to serve only as a passage-way for the food. A similar picture is also presented by linitis plastica.

It must be stated, with emphasis, that there are cases in which a differential diagnosis between achylia gastrica and carcinoma is impossible by means of the roentgen ray. These are the cases in which the posterior wall of the stomach alone is involved.

In a certain number of cases, as pointed out by Th. Hausman,[29] achylia gastrica with all the clinical symptoms results on the basis of syphilis. Here the Wassermann reaction and the Noguchi-Luebin reaction will aid a great deal. The importance of the Noguchi-Luebin reaction in syphilitic affections of the stomach is confirmed by F. Smithies[30] in a large number of cases.

It still remains for us to differentiate achylia gastrica resulting on the basis of secondary or primary anemias. The achylias resulting from secondary anemia are determined by establishing the etiological factor (intestinal parasites, metallic poisoning, gout, diabetes, etc.). More important to differentiate is that form of achylia associated with primary pernicious anemia. In these cases a real anadeny exists. The blood picture is the most important diagnostic aid, inasmuch as it shows that we are dealing in the anemia with a hemolytic disease and not with one of digestive disorder. The leading points are: high color index; poly- and hyperchromatic condition of the red blood cells; leukopenia; diminution or absence of blood platelets; diminution of resistance of red blood cells. The work of Eppinger as well as that of J. P. Schneider[31] demonstrating urobilinogen and urobilin. In the chocolate-colored duodenal contents will also serve to demonstrate that the achylia gastrica is secondary to the anemia.

In the diagnosis of achylia we must not overlook the differential diagnosis between it and heterochylia (Hemmeter[32]). By heterochylia we understand a condition in which the gastric secretions show a great tendency to changes in value of acidity. One examination may show a complete achylia and another examination, after a shorter or longer interval, may show even a hyperacidity.

If we meet with a heterochylia during the state of achylia and

[29] Ergebn. f. inner. Med. im. Kinderheilkund., 1911, vi, 279.   Th. Brougsch and Schneider, Berl. klin. Wchnschr., 1915, p. 601.
[30] Arch. Int. Med., January, 1916.
[31] Jour. Am. Med. Assn., August 14, 1915.
[32] Diseases of the Stomach, 1902.

examine the stomach contents of the same patient a few weeks later and find a normal or even a higher acidity we may be misled to attribute the change to the therapeutic effect. The mode of clearing up the differential diagnosis is subject to time. Heterochylia, as pointed out by Hemmeter, shows changes in the acidity values, and the patient has corresponding complains.

Complications. The most important complication is a resulting organic disturbance of the intestines. The primary diarrhea because of the existing hypermotility in the small and large intestine may eventually lead to fermentative diarrhea and later to catarrh of the small and large intestine.

A rare complication is brought about by the absorption in the blood of toxic proteins, the result of the loss of vicarious digestion on the part of the small intestines. Anaphylactic phenomena and gastro-intestinal disturbances grouped by Vaughn as protiosis occur.

Some authors claim that carcinoma may arise on the basis of an achylia. Pernicious anemia, claimed by Grawitz and others to be the result of achylia, does not seem plausible. As already stated above it is rather to be assumed that the achylia is the result of pernicious anemia.

PROGNOSIS. In the functional achylia gastrica prognosis as to life is favorable; the majority of patients even enjoy fairly good health throughout the greater part of their lives. Prognosis as to recovery to normal is unfavorable. Very few cases are reported in which gastric secretions have returned. Achylia gastrica on the basis of lues has a more favorable prognosis as to the return of secretions according to Brugsch and Schneider. According to Lockwood, cases of achylia associated with gall-stones and appendicitis are improved on the removal of the cause.

TREATMENT. Treatment must be strictly individualized, and for the sake of clearness, cases should be separated from the therapeutic stand-point into the following groups:

1. When the symptoms point to a general neurosis with corresponding gastric symptoms. The discovery of achylia in such patients must not lead us to believe that the cause of nervousness has been discovered and that the proper therapeutic measures against achylia will have a favorable influence on the nervous system. In the great majority of cases the reverse holds true. The achylia is the expression of a general neurosis and the treatment must therefore be directed against the nervous system with moderate and appropriate attention to the stomach. Such patients should lead a most regular life, both physically and mentally; they should avoid toxic agents like tobacco and excessive alcohol. Therapeutic measures should be employed, depending upon the general condition of the patient. Robust people should be advised to take once or twice a week some form of sweat bath (box bath or Turkish or electric bath), also a

morning shower. Weak people should take half-baths of 98° to 100° F. temperature with friction of the chest while in the bath and a cold towel on the head, the procedure to last from ten to fifteen minutes, after which water of lower temperature, 90°, is to be poured over the spine. With some patients the cool pack for from a half to an hour is more effective. When the patient can afford frequent and short vacations, either seashore or mountains are very beneficial. For the gastric symptoms a spa containing the sodium chloride waters (Saratoga, Hot Springs, Kissingen, Homburg, Dresden, Tarasp) for one month is very beneficial. In choosing such a spa it is essential to call the attention of the local medical adviser to the existing neurosis so that not the drinking of the waters shall play the main role, nor even the diet, but the general measures to tone up the nervous system shall be of prime importance.

The dietetic régime should not be so strict as to make the patient everlastingly dependent. In a general way we direct him to reduce the daily quantity of meat. He must be told to chew hi food well. In this affection thorough chewing almost to the extent of Fletcherizing is of the utmost importance, for as the pylorus is open and as the food passes through the stomach quickly, poorly chewed food serves as an irritant to the small intestine. It is evident that proper attention should be paid to the teeth. Spices in moderation are beneficial (pepper, also cinnamon, salt, caviar, vanilla, orange peel, etc.). Of the liquors a light sour wine with the meals is useful. Lemonade, Billiner waters, Saratoga sparkling water, and sour drinks are preferable to plain water.

To the second group belong cases in which the gastric symptoms predominate (continuous burning right after meals, pressure, and even pain). The symptoms may be so distressing and persistent, and, due to the fear of eating, even cause some loss of weight, that an understanding of the exact nature of the disease is most trying. Lockwood even goes so far as to state that these pains are of extragastric origin (cholelithiasis, appendicitis) and that the removal of the cause would cure the achylia. This does not correspond to our experience. We are rather inclined to think that the persistent and severe symptoms are likewise exaggerated because of the underlying neurosis. That removal of the extragastric disease improves the symptoms of achylia does not prove that this was the cause of the disease, because we know that neuropathic individuals often get well after an exploratory laparotomy, although nothing was found at the operation. All this is stated with the object of showing that while in this group of cases our dietitic and medicinal régime must be more carefully outlined, we must not lose sight of the psychical part of the treatment.

The diet must be guided according to the following principles: The food is prepared sufficiently so as not to be a burden to the intestines mechanically, and must also be of a nature to depend least

on stomach digestion and at the same time not to irritate the small intestine.   It is best to divide the dietetic treatment into two parts—that of sparing the digestive organs and of exercising those organs. The sparing diet must be individualized as to the kind of food and the length of time such is to be carried out, depending on the severity of the symptoms.   When these are very distressing it is necessary to keep the patient on warm milk, cream, and yolks of eggs for the first four or five days, then gradually progress to thin cereals prepared in milk, toast, and butter up to the end of the first week, during all of which time the patient should remain in bed.   When the symptoms have considerably diminished we can add bouillon with egg, beef soup, and of the vegetables first mashed potatoes with butter, because they are best borne, then spinach, asparagus tops, string beans, etc., all passed through a purée sieve.

During the second week two or three eggs may be given daily, and the cereals in the form of light puddings or custard.   If the patient is fairly comfortable in the second week, noodles and macaroni may be added to the diet.   With meat we should begin gradually, and then only with finely scraped or chopped meat well done.   Spices and alcoholic beverages should not be allowed while the acute symptoms last.   When the symptoms are not of such a severe nature we can at once proceed with a diet corresponding to that described for the third week in the severe cases.

The exercise diet should not begin until the acute symptoms disappear, and even then not abruptly, so as to avoid a recurrence of symptoms, thereby undermining the self-dependence of the patient.

The following list is a fair and sufficient example of what an achylic patient should partake of and be fairly free from disturbance, and at the same time allow him enough variety.   The dietetic mode of life for a great length of time of an achylic patient who is subject to gastric symptoms should be the following: In the morning, on an empty stomach, about three-quarters of an hour before breakfast 250 c.c. of hot water to which a half teaspoonful of Nachlorat is added.   Breakfast: orange juice or grape fruit, then eggs in any form, with the exception of hard-boiled eggs, cocoa or light coffee or tea, Graham bread or rolls with butter.   Two or three times a week we replace the eggs by cereals, mashed potatoes, noodles, macaroni, or cream cheese.   Dinner: grape fruit or caviar or anchovies, sardines, sardelles as appetizers, then some bouillon or beef soup or well-prepared vegetable soup mildly spiced.   Of the meats either fish, chicken, lamb, veal, or cooked ham, calf's brain, fresh sweetbread or even steak can be given, but thorough chewing is essential besides the proper preparation in the kitchen (well done and finely chopped and mildly spiced with onions, salt, and pepper).   Of the vegetables, those named above and a cereal or noodle pudding or omelette, or prune soufflé and cooked fruits.   At 4 P.M. one cup of buttermilk with zwieback or toast and butter.   Supper: like break-

fast, with the addition of some cooked fruits, and buttermilk should replace the coffee.

Severe cases should rest in bed the first week and hot poultices should be applied to the abdomen. If these do not relieve the pain small doses of dionin (gr. 0.01) or pantopon (0.1), two or three times daily, may be given, and in order to secure a restful night, veronal (0.5) in suppositories or adalin (0.5) by mouth may have to be resorted to for a few nights. The bowels should be kept open by a daily salt enema or by an occasional dose of calomel (0.2) in one dose. Should marked nervous symptoms exist during that time a cool sponge bath or cool packs or, as a last resort, bromides in the form of atrontium or sodium bromides (0.6) twice a day may be given.

For bad taste in the mouth one should, besides the antiseptic mouth washes, have the patient use some pleasantly flavored chewing-gum or, as Schule advises, have him chew peppermint leaves, orange peel, or rhubarb root.

A bad taste in the mouth and distention are frequently remedied by a teaspoonful of rhubarb and soda, to be taken three times daily. If meteorism is a disturbing symptom an infusion of peppermint tea (1 to 250 c.c.), taken hot on retiring, is beneficial.

As improvement progresses a more liberal diet is partaken of, the amount of rest depending on the physical condition of the patient chiefly and to some extent also on circumstances. When the patient can afford to do so it is best that he return to routine work very gradually; but if he is to follow up his occupation he must be advised to reture at an early hour and rest after his chief meal for at least half an hour. Hydrotherapeutics in the form of mild douches or warm baths, in the summer season sea baths, are very beneficial.

Medicinally the most important part is the HCl and pepsin:

Acid. hydrochlor. dilute.,
Pepsini puri . . . . āā 5 10
Aquæ 50 100
S.—One teaspoonful in a glass of water, to be taken before and during the meal.

It may also be given in the form of acidol-pepsin tablets (No. 1 or 2, weaker or stronger), one dissolved in a tumbler of water thrice daily with meals. We are fully aware of the fact that HCl and pepsin do not exercise their beneficial effect by replacing the missing secretions, because they cannot be given in quantities large enough to bring about such an action without having a local and generally poisonous influence, and the secretions cannot be made to return in true achylia. The fact, however, that we clinically see improvement by HCl and pepsin must depend on the improved motility brought about by the above-named drugs. Because of the acid introduced into the stomach the pylorus remains closed for a longer time, the closure and opening of the pylorus depending on the Hirsch-Nehring-Pawlow-Cannon reflex occurs more regularly. Acid even in small

quantities excites peristaltic action, thereby mechanically influencing digestion.

When patients complain of loss of appetite it is still customary for some empirically to prescribe the so-called stomachics and amara (tet. mucis nam; extr. fluid. condurang.; mixtur. cuichon. comp.). As to the usefulness of these amara extreme views exist. From the stand-point of the physiological experiments of Carlson[33] and others the stomachics are not only beneficial but they are injurious, inasmuch as they diminish secretions. Many clinicians of great experience (Ewald, Boas), however, still claim favorable results. The ideal stand-point in exciting the appetite is taken by Wm. Sternburg, who states that the proper preparation and variety of food are the best means to that end.

In the gastric type of achylia gastrica, unlike the pure neuropathic type, saline mineral waters either at the spas or at home should be employed once a year for four weeks in the quantity of 250 c.c. taken hot in the mornings one hour before breakfast and one or two hours before supper. These waters do not exercise any curative influence on the achylia gastrica, but they bring about considerable improvement. That the waters taken at the spas have a better effect than when taken at home is due to the proper diet, pleasant surroundings, regular mode of life, and well-carried-out physicotherapeutics by trained men. It should be borne in mind that these patients have a tendency to be hypochondriac and proper psychical influence is most important.

When there is a marked tendency to constipation a course of olive-oil enemata lasting from two weeks to a month should be employed, and repeated in the course of intervals as the case may necessitate.

To the third group of cases belong those in which diarrhea is the main symptom. In a number of cases the discovery that the diarrhea is due to achylia gastrica gives us an encouraging hint that the diarrhea will be favorably influenced by the proper treatment. The treatment, however, must be individualized. Patients who have not the symptoms and signs of enteritis are benefited readily by the removal of the milk, by interdicting meat for a few days, and then gradually returning to well-done and finely chopped meat, not exceeding 200 to 250 grams a day. Raw fruits and coarse vegetables (beans, cabbage, lentils, etc.) must be forbidden. The diet consists of eggs, water cocoa, fine cereals (rice and barley in particular), with butter, toasted white bread, macaroni, fish, and cream cheese, and three-day old kumyss. Of the drinks red wines are beneficial. Medicinally, HCl and pepsin in the formula given above with and after meals and calcium citrate or calcium phosphate

[33] Jour. Am. Med. Assn., January 2, 1915; Jour. Phar. and Exp. Therap., November, 1914.

(Boas) in teaspoonful doses in a tumbler of water before meals are beneficial.

In more obstinate cases of diarrhea, and especially when the symptoms point toward enterocolitis, the diet should be restricted to strained barley soups, water cocoa, tea, rice, or sago soups cooked in water to which cinnamon is added for the taste, and almond milk. Almond milk is prepared as follows: Forty sweet almonds and two bitter almonds are placed in boiling water for a few minutes; then the almonds are peeled and ground. Add half a pint warm water, stirring constantly, and pass through a cloth. It should be allowed to stand on ice for two hours before drinking, and should be freshly prepared every day. One hundred grams of red wine are allowed in the course of the day. Such a diet is to be continued for three or four days, during which time the patient should stay in bed with hot poultices or a Prissnitz compress applied to the abdomen. Medicinally we start with 20 grams of castor oil, followed by tannigen 0.2 to 0.3 or tannalbin 0.5 two or three times daily. If there is still intestinal irritation saline enemata (2 teaspoonfuls to a quart of water) or an infusion of chamomile tea (1 to 2 teaspoonfuls to the quart) will prove beneficial. The return to a more substantial diet should be gradual. For at least one month the following diet list will prove efficacious:

Breakfast: One or two soft-boiled eggs, 4 slices toast or zwieback with butter, 250 grams water cocoa to which one or two yolks of eggs are added.

At 10 a.m.: One cup bouillon

At noon: Barley or rice soup; spring chicken or lean fish. Vegetables: 2 tablespoonfuls finely mashed potatoes or spinach or carrots in purée form. Should even these vegetables prove irritating the quantity should be diminished or removed. On the other hand if the patient stands it well we increase the quantity of vegetables. Farina pudding and 60 grams red wine.

At 4 p.m.: 250 grams almond milk or water cocoa with zwieback.

At 7 p.m.: One or two eggs; cereals with butter or barley soup. Oatmeal and barley should be strained. Toast and butter. Water cocoa with yolk of one egg. HCl and pepsin in the formula given above are beneficial, while stringents will probably not be necessary. Should, however, the enteric symptoms persist it is evident that we are confronted with an infectious enterocolitis either brought about, as claimed by Ad. Schmidt, by increase in the existing colon bacilli, or by the colon bacilli changing into virulent organisms, or the existing pathogenic organisms because of the favorable soil and the lowered resistance of the patient gain the upper hand. In this state mild astringents and intestinal antiseptics are necessary. The efficacy of astringents like bismuth subnitrate (0.5 to 1), or dermatol (0.5), tannigen (0.3), tannalbin (0.5), three times daily, is well established. The usefulness of intestinal antiseptics was rightfully disputed by

pharmacological experimentation and clinical results.   It was shown that small doses have absolutely no effect while doses large enough to be effective are poisonous, and hence the large group like salol, resorcin, ichthyol, menthol, etc., have been discarded.   Recent experiences in the present war with the infectious enterocolitis cases have brought forward the mode of administering large doses of intestinal antiseptics, bringing about a curative effect without injurious results.   It was found that when drugs like kaolin (bolus alba, or fuller's earth)[34] or animal charcoal are given half an hour before the meal and the intestinal antiseptic half an hour after the meal not only is an absorptive effect on the bacteria and toxins achieved but the slow and minute absorption of the antiseptic into the blood is prevented by the charcoal or kaolin.   In other words the antiseptic has its local effect and the rest is eliminated through the bowels with the absorbent substances.

The antiseptic chosen was thymol in doses as large as 0.5 to 1 three times daily half an hour after meals.   Of course, other antiseptics, especially β-naphthol or resorcin, may be employed in the same manner.   Caution as to the use of large doses of thymol is important. It should be begun with 0.3 to 0.5, and only when such doses are not effective may it be increased.   Absolute constipation should be prevented by an occasional dose of castor oil, and the antiseptic should be discontinued as soon as the patient improves, because the prolonged use of thymol has a deleterious effect on the intestinal ferments.   For cases in which the symptoms point toward a pancreatic disfunction (achylia pancreatica) we should, with Wahlgemut, restrict carbohydrates for a time; otherwise the diet list is the same as the one outlined above for achylic diarrhea.   Medicinally, pancreon 0.5 three times daily after meals should be employed.

Rehfuss[35] has obtained results with parathyroid, one-tenth of a grain t. i. d., given for three-day intervals.

INDICATIONS FOR BLOOD TRANSFUSION.

By George Morris Dorrance, M.D.,

PHILADELPHIA.

To simplify the discussion and condense the indications, I shall divide the conditions in which transfusion is necessary into classes and take up each class separately.

First class: Acute traumatic hemorrhage, both internal and external.   This, of course, includes secondary hemorrhage.

[34] Hess: Jour. Am. Med. Assn., January 8, 1916.
[35] Am. Jour. Med. Sc., July, 1915, p. 72.

Second class: Hemorrhagic obstetrical complications.

Third class: Shock.

Fourth class: Hemorrhage from the viscera.

Fifth class: Anemia in non-malignant conditions.

Sixth class: Anemia in malignant conditions.

Seventh class: Anemia in tuberculosis.

Eighth class: Anemia in infectious diseases.

Ninth class: Blood dyscrasia.

Tenth class: Hemorrhage of the newborn.

Eleventh class: Poisoning.

Twelfth class: Delayed coagulation time.

1. Acute traumatic hemorrhage, both internal and external. This, of course, includes secondary hemorrhage. In just what degree of anemia in traumatic hemorrhage is transfusion necessary? This will have to be determined somewhat by the associated clinical symptoms, such as shock, etc. It may be said that with a blood count of 1,000,000 red blood cells and hemoglobin of 20 per cent. or below there is an absolute indication for transfusion, but when the count is 1,500,000 red blood cells and the hemoglobin above 25 per cent. it may or may not be employed, depending upon the associated symptoms. The above holds good for secondary as well as primary hemorrhage. It is, of course, assumed that the bleeding-point is controlled or can be controlled, as in hemorrhage from ruptured liver or spleen.

2. Hemorrhagic obstetrical complications. Postpartum hemorrhage, whether it is due to delayed coagulation time or not, has been one of the main indications since the earliest times of transfusion. In just what degree of hemorrhage it is necessary is questionable, and just the amount of blood required is difficult to determine. In the first place the rule as given above, of 1,00,000 or below, is an absolute indication, and 1,500,000 as a questionable indication holds good here. Hemorrhage in placenta previa or premature detachment may or may not require transfusion, depending upon the rapidity of the obstetrician, meaning of course, the loss of blood and associated shock. Transfusion is absolutely indicated if the count is below 1,000,000 or when there is associated shock, pallor, air hunger, etc. It often makes it possible to operate upon cases in which otherwise they would have died from cerebral anemia. It is absolutely indicated in cases of this type with greatly increased coagulation time.

3. Shock. In surgical shock *per se* without hemorrhage it is not as valuable as salt solution and adrenalin, but in shock associated with severe hemorrhage it is of decided value. Just what degree of shock in hemorrhage indicates transfusion must be determined in each case.

4. Hemorrhage from the viscera. In anemia from gastric hemorrhage, if hemorrhage producing the anemia was due to ruptured

varicose veins—a complication of cirrhosis of the liver—transfusion is contra-indicated, as it will only increase the hemorrhage by raising the blood-pressure; but if the anemia is a complication of an ulcer or postoperative bleeding from gastro-enterostomy, transfusion should be performed and immediately followed by abdominal section to control the bleeding-point. Of course, it has been assumed that the hemorrhage has been of sufficient severity as to cause a grave anemia. If the hemorrhage is from the intestines, as in typhoid fever or tuberculous ulcer, it may or may not be of decided value; but here the transfusion should be in small amounts, and frequently repeated so as not to increase the blood-pressure and thereby start the bleeding.

5. Anemia in non-malignant conditions. In non-malignant conditions or tumors in which on account of frequent small hemorrhages the patient is considered a bad operative risk he may be made a good operative risk by transfusion. This will, of course, allow of wide interpretation. Examples of conditions such as fibroid tumors, papilloma of the bladder, hemorrhoids, etc. In renal hemorrhage, whether of essential or other type providing the anemia is sufficiently severe, it is indicated as a preparatory treatment preliminary to operation.

6. Anemia in malignant conditions. In this condition at one time it seemed from experimental studies that there was going to be a large and brilliant field. This, however, under the clinical test has proved to be erroneous. It has practically no effect upon the course of the malignancy, and is only indicated as a means of overcoming the anemia as a preparatory stage for other treatments.

7. Anemia in tuberculosis. Here as in malignancy it has been frequently used to control the tuberculosis instead of being used, as it should be, as a means to overcome the anemia. In pulmonary hemorrhage it is usually not indicated, but in very severe types of anemia from this case transfusion may be used in small repeated transfusion, being careful not to increase the blood-pressure and start up the bleeding. As a preliminary procedure to operation upon any tuberculous subject who has been a severe anemic it is, of course, indicated. In miliary tuberculosis it has no effect upon the disease.

8. Infectious diseases. In infectious diseases, such as typhoid fever, scarlet fever, etc., it is of no value. In cholera it has been said to be of decided value on account of the rapid loss of fluid and the subsequent anemia. I have had no personal experience with it. In acute sepsis no permanent results have been noted by careful observers. In pellagra various results have been recorded, some claiming wonderful results, others condemning it. As I have had no personal experience, I must depend upon the published results. It could at least be said that there are no deleterious results, and there has been some temporary improvement. In infectious diseases then it can be said that there is no specific effect upon the

infection by the transfusion, but if any anemia is present it is temporarily improved.

9. Blood dyscrasiæ. In hemophilia it will have the effect of correcting the anemia, and if given in sufficient amounts will usually cause the coagulation time to approximate the normal. The effect upon the coagulation time, however, is usually only of value for a short time, and only in exceptional cases does it have a permanent effect in overcoming the delayed coagulation time. In pernicious anemia the results have been very discouraging, and at times very satisfactory. As this disease tends to have remissions, it may be that if transfusions were performed on the upward curve the results would have been more permanent and satisfactory. The least that can be said is that a limited number have been cured, many have been benefited, and there ought not to have been any injured. The transfusion should be repeated several times at approximately weekly intervals. It is of decided advantage in preparing these patients for removal of the spleen. In leukemia several cures have been reported by repeated transfusions, as has also several unfortunate calamities. I have no personal experience, so must depend upon the reports of others. It is one of the blood dyscrasiæ in which I do not think transfusion is indicated. In splenic anemia and Banti's disease it is only of value as a method for correcting the anemia or as a preparatory measure for splenectomy.

10. Hemorrhage of the newborn, melena, etc. In most of these cases, serum or defibrinated blood is all that is necessary, but in very severe anemia it is indicated, as it is the only treatment that will benefit these cases; but the pathology of these cases must be remembered, that is, frequently there are large hemorrhages into the lungs, liver, etc., before there are any external signs of bleeding. The pathology, of course, accounts for why a certain percentage of these cases die after transfusion. In any case, care should be exercised in giving more than a moderate amount, and this under low pressure to prevent dilatation of the right heart.

11. Poisoning. In gas-poisoning, illuminating and otherwise, it is of limited value and should only be used after very severe vena section, as it is the toxemia and not the anemia that is the point to be corrected. In poisoning from coal-tar derivatives with the chocolate-colored blood it will be found that a severe vena section with salt solution will usually give results equal to transfusion. In the metallic poisoning I have not seen any results. In acute bichloride-poisoning, however, I have been tempted to perform large vena sections and transfuse large amounts, but have not seen a suitable case.

12. Delayed coagulation time. In delayed coagulation time from whatever cause it is frequently on account of the severe anemia desirable to overcome the deficient coagulation time rapidly, or it may be that one or more of the constituents of the blood, such as

fibrinogen are absent and blood serums or blood placquelets, will not give the desired results. In this condition it has the double effect of correcting the anemia and shortening the coagulation time.

The indications for transfusions may then be practically summed up in the following manner: It may be used in any condition to correct a very severe anemia or it may be the only method of rapidly controlling a lengthened coagulation time.

DIABETES INSIPIDUS.

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Our knowledge of diabetes insipidus at the present time is well examplified by the fact that of those who have given careful consideration to this pathological manifestation, some call it a "disease" while other authorities prefer to designate diabetes insipidus as a "disease syndrome." Diabetes insipidus is of comparatively rare occurrence, being about 14 in 100,000 patients. One therefore approaches each new case with interest, and with the hope of finding a clue to its etiology and proper treatment.

In a very interesting study, Fitz[1] calls attention to the fact that diabetes insipidus was recognized in 1682 by Thomas Willis, and well described by Johann Peter Frank in 1794, and it is remarkable that so little information has been gathered since that time. This, however, may be due to the fact that diabetes insipidus does not have a definite anatomical basis, or if it does, it certainly has escaped detection. In more recent times the problem of diabetes insipidus is being approached by the avenue of functional pathology, and results seem more promising.

Diabetes insipidus may be defined as a disease state characterized y an excessive polydipsia and polyuria.

According to various observers it has been known to occur when there was an hereditary tendency to the disease; it has been known to occur after fevers, after physical injury to the brain and cord, after psychic trauma, after luetic disease of the nervous system (particularly basilar meningitis), after tumor of the brain, and after tumor or irritation or injury to the hypophysis, such injury being accidental or following surgical interference, and also after injury to the temporal region of the brain, and particulrly after injury in the region of the floor of the fourth ventricle. Diabetes insipidus has been known to occur in cases of carcinoma of the liver and of the adrenals (by metastasis?), and in disease of the pancreas.

[1] Arch. Int. Med., 1914, xiv, 706.

It will be of interest to cite the tendency of modern opinion held by those who have studied this condition. Allen[2] says: "In general there seems to be ground for believing that diabetes insipidus belongs among the disorders of internal secretion. The facts are not yet sufficient to warrant a conclusion or hypothesis."

Falta[3] states: "We must leave the genesis of the disease open." Fitz holds: "On the whole it appears that diabetes insipidus is usually of the symptomatic type, though it may be of the idiopathic. The exact cause of the polydipsia and polyuria is undetermined. Certain observers believe that the concentrative powers of the kidneys are at fault, others that the polyuria results from an abnormal thirst." Barker[4] likewise holds the view that there are two forms of this disease: the idiopathic diabetes insipidus, due to a functional disturbance of the kidney, which makes them incapable of secreting a concentrated urine, and the symptomatic diabetes insipidus, in which there is no functional insufficiency of the kidneys. The polyuria is secondary to a primary polydipsia, this latter type being of neurogenic origin or due to some disturbance of internal secretion.

The case reported by Fitz showed that the kidneys were capable of performing a normal amount of work, but there was a particular sensitiveness to salt. The ingestion of 25 grams of sodium chloride brought on a marked diuresis, "vascular hyposthenuria."

The case to be reported here will be presented from the standpoint of functional capacity of the kidney, whether the kidneys were hypersensitive to urea, chlorides, and glucose, and to record those other observations which time and circumstance permitted. Excepting for one day in the hospital the patient was an ambulatory case, and it required much tact to procure the observations which I was permitted to make, as he had already seen many physicians, and did not care to lend himself to extended observations.

CASE HISTORY.—W. C. B., male, aged forty-eight years; family history is good; previous health good. No history of venereal disease, accident, or trauma. In August, 1912, had an attack which his physicians designated congestion of kidneys; recovery was good. Eighteen months ago, independent of everything else, he developed polydipsia and polyuria, but no polyphagia. Fourteen months ago had an attack of "grip," followed by exsiccation and exfoliation of skin and mucous membranes. Since the onset of polyuria he has been passing from 6 to 11 quarts of urine daily. Five years ago he weighed 175 pounds, six months ago 190 pounds, and now weighs 195 pounds; so that, irrespective of the polyuria, his body weight has increased and his nutrition is apparently unaffected.

He follows his occupation, cattle rancher, which entails much

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[2] Glycosuria and Diabetes, Harvard Univ. Press, 1913, p. 523.
[3] The Ductless Glandular Diseases, Blakiston, 1915, p. 323.
[4] Monographic Medicine, iv, 815.

physical exertion, and frequently hardships. His diet is that of many American workmen, high in protein. He eats eggs, fruit, and coffee for breakfast; meat, vegetables, dessert, and coffee for luncheon; soup, meat, vegetables, coffee, and dessert for dinner. His physical comfort varies with his ability to get water.

In the foothills of the Rocky Mountains, for a distance of forty miles from the Main Divide, he nearly always manages to get a supply of good water while crossing streams, at least once in three hours. But when he gets in the low country, where the soil and the water are both rich in alkali, he suffers much inconvenience. The alkali water and the sulphur waters are undesirable for drinking, and with him, as with the other men, it frequently causes an irritability of the bladder.

Physical Examination. Height, 5 feet 6 inches; weight, 195 pounds; general type, robust. Skeleton and features normal. Head and neck negative. Vision normal. Radiograph shows a normal sella turcica. Chest: lungs negative, heart negative. Blood-pressure: maximum, 156; minimum, 97; pulse, 84. Abdomen negative. Extremities negative. Reflexes normal. Glands negative. Gastro-intestinal history negative. Nervous system negative. Circulatory history negative. Blood count normal. Wassermann negative. Urine shows trace of albumin; no casts.

Water Excretion. The patient did not lend himself to the water test, as his thirst seemed unsatiable. He would not or could not control the thirst sufficiently to permit a starting-point for the test, aside from the difficulty he would have had in taking an amount of water greater than he was already drinking.

His average excretion was 500 c.c. to 600 c.c. per hour.

Polydipsia. This was the patient's chief complaint, his inordinate desire for water, and it was, as he said, not because of his need for the water, which when it reached his stomach made him feel oppressed and uncomfortable, but that he craved the water to allay the horrible "leathery" taste in the roof of his mouth, pharynx, and back of his tongue. Abstinence from drinking made him feel that his parched tongue would stick to the roof of his mouth and the back of his throat." Even copious rinsing of the mouth did not relieve him. This parageusia may indicate an alteration in function or structure of the glossopharyngeal nerve or central involvement at the medulla. Blocking of that nerve would have been an important experiment in this case had it been possible.

Hyposthenuria. For a period of one month, during which the patient kept careful account of his daily urinary output, the maximum was 12,450 c.c. and the minimum 11,000 c.c., the average secretion being 11,670 c.c. per day. During a period of three days, on a constant diet, the patient received successively 20 grams of urea, 10 grams of salt, and 100 grams of glucose. After the urea he excreted 13,396 c.c., after the salt 13,110 c.c., and after the glucose

12,930 c.c.; so that in response to the increased presence of these substances in the blood we find there was greater demand for water and a larger urinary excretion.

Conversely, when the patient was placed on a Mosenthal salt-free diet the total excretion within the following twenty-four hours decreased promptly from 12,930 c.c. to 10,500 c.c., a fall of 2430 c.c. in twenty-four hours. How the kidneys responded to each one of the substances separately will be referred to later.

Specific Gravity. This varied between 1000 and 1003; the latter concentration was attained on the day the urea was taken.

Urea Excretion. In the twenty-four hours following the ingestion of urea the specific gravity rose from 1001 to 1003, and the entire 20 grams of urea were eliminated. This shows a definite ability on the part of the kidney to concentrate urine. The urinary output was 13,396 c.c., evidencing a greater than average desire for water and proportionate elimination. There was no hypersensitiveness to urea.

Salt Excretion. After 10 grams of salt given on the day following the urea the total volume of urine was slightly diminished; the specific gravity was 1001. The salt was eliminated promptly as the urea was, 9.4 grams in the twenty-four hours. There was no hypersensitiveness to salt.

Glucose. Four and a half hours after supper 100 grams of glucose were taken. This was followed by a diuresis of 2640 c.c., which kept him awake during the next four hours. A portion of this four-hour specimen of urine reacted positive to Benedict's, Almen-Nylander's bismuth test, and produced fermentation. Quantitatively, the amount was too small for estimation.

That glucose does not ordinarily produce a diuresis was shown by Taylor and Hulton,[5] who administered from 200 to 50) grams of glucose in twenty normals and rarely found a diuresis.

Hydrogen Ion Concentration of the Urine. As tested on several occasions I found to methyl orange the reaction was alkaline, to methyl red it was alkaline, to phenolphthalein acid and to Kahlbaum's neutral litmus it was slightly acid.

The hydrogen ion concentration of the urine may therefore be recorded as being 10 to 9, or about normal.

Salt-free Diet. Placing the patient on a Mosenthal salt-free diet resulted in a prompt decrease of 2400 c.c. urine during the following day. The salt elimination was moderately diminished and urea was decreased by exactly half of the previous day.

Phenolsulphonephthalein Output. Dye appeared in ten minutes. At the end of the first hour there was 600 c.c. of urine, specific gravity 1004, and dye elimination 16 per cent. Total phenolsulphonephthalein elimination, 69 per cent.

5 Taylor and Hulton, Jour. Biol. Chem., 1916, xxv, 173.

Lumbar Puncture. Upon entering the spinal canal the fluid came through the needle in a steady stream, which had not diminished when 25 c.c. was removed. I thought it inadvisable to remove more, and stopped. There was no increased pressure behind the flow, and I looked upon this as being one phase of the general flux of fluids in the body of this patient. This may prove to be an important observation that in some cases at least the greater liquid exchange is not limited to the kidney.

On the day preceding lumbar puncture the urinary output was 12,000 c.c.; on the following day, the patient having been kept in bed, it was 7950 c.c.; on the next day the patient was up and about, and it was again 12,000 c.c. Lumbar puncture had no more than a transitory if any influence upon the polyuria. No cells were to be found in the fluid. The globulin test was negative, sugar reaction slight, and the Wassermann in quantities of 0.2, 0.4, and 0.8 c.c. was negative. I now believe that we should have used much larger amounts of the spinal fluid as well as the blood for Wassermann tests on account of the high dilution of the body fluids.

Saliva. Upon examination of the mouth it was readily seen there was a copious salivary flow, as the saliva trickled down the inner cheek from the mouth of Stenson's duct in a continuous stream. The salivary secretion from the sublingual gland was likewise profuse. To Kahlbaum's neutral litmus the reaction was acid. We may account for the sialorrhea in several ways: (1) as with urinary flow and the spinal fluid, the liquid exchange or flow through organs which normally secrete a fluid is abnormally large; (2) that the sialorrhea is physiological and occurs in response to the parageusia through stimulation of the parotid gland; (3) that the sialorrhea is pathological and is the product of an abnormal stimulation or disease of the nerves governing the function of the gland, glossopharyngeal, or its centre in the medulla. The salivary glands are sensitive to stimulation, $\frac{1}{5}$ grain of pilocarpin markedly increased the already large flow of saliva.

Drugs. Without going into details of the pharmacological action of these drugs I merely note the effect of the following drugs:

Atropin, grain $\frac{1}{50}$ t. i. d. for four days, caused no change in amount nor concentration of urine.

Sodium nitrate, gr. iij, q. i. d., no effect.

Potassium bromide, gr. 10 q. i. d., no effect.

Pilocarpin, gr. $\frac{1}{5}$ produces a marked diuresis lasting two hours, during which time there is eliminated 500 to 1000 c.c., more urine than is normal for him. After two hours there is a decrease, also lasting two to three hours, after which time the normal rate of flow is resumed.

SUMMARY. A case of diabetes insipidus with kidneys capable of eliminating a normal amount of solids in the twenty-four hours. In response to ingestion of added amounts of salt and urea the

kidneys show ability to eliminate these substances promptly and to concentrate urine. In response to the ingestion of 100 grams of glucose the urine showed a trace of sugar and a diuresis followed. Phenosulphonephthalein elimination was normal. There were evidences in this case suggesting that the abnormally large liquid exchange was not limited to the kidneys, but that the spinal fluid and saliva were likewise secreted in abnormally large amounts.

It was demonstrated that although the kidneys and salivary glands were already performing an inordinate amount of work, as far as excretion of water is concerned they were not functioning to their maximum capacity.

Pilocarpin produced a sialorrhea and diuresis after each dose on several days. Circumstances did not permit any attempt at determining the part played by the internal secretions in this case, nor was it possible to make any observations toward determining the part played by the glossopharyngeal nerve in the polydipsia.

THE METASTASIS OF TUMORS: A STUDY OF 298 CASES OF MALIGNANT GROWTH EXHIBITED AMONG 5155 AUTOPSIES AT BELLEVUE HOSPITAL.

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There are reasons for believing that as a result of accident or other fortuitous circumstance, or even in the ordinary course of events, certain fixed cells may become liberated into the circulation, e. g., placental cells may be freed and transported to the liver, and liver cells may be released and carried to the lungs. In either event proliferation of the transplanted cell is obstructed not only by equilibrium of function in the cell itself, but by the innate antagonism of the tissue in which it finds lodgment. There are equally acceptable reasons for believing that the cells of certain tumors are more or less constantly discharged into the blood stream and destroyed. Seldom is this destructive property placed in abeyance, as is evidenced by the rarity of universally disseminated metastases in human tumors and by the low proportion of successful inoculations following injection into the blood stream of emulsions of the transplantable tumors of lower animals. The lymph stream, on the contrary, seems to be devoid of inimical properties, and the tumor cell, particularly the epithelial variety, not only

obtains hospitable lodgment in the lymph spaces, but finds conditions favorable for its growth.

The quality of anaplasia and the capacity to infiltrate and metastasize combine to form the most dependable of the several criteria by which the malignancy of a tumor is judged. There are instances, however, in which misplaced groups of cells are not only suspiciously arranged, but exhibit distinct anaplastic peculiarities together with a noticeable disposition to remain circumscribed and at rest. For example, there is a carcinomatoid formation occasionally to be seen in the lower end of the small intestine that possesses marked anaplastic features, and, from the general appearance of a given microscopic field the pathologist would be entirely justified in pronouncing the growth malignant, yet local expansion seems seldom to trespass beyond bounds, and metastasis is practically unknown. A closely related variety of growth is not infrequently encountered in the appendix and is likewise of little significance.[1] The same, in part, is true of the pigmented cutaneous mole, the histological structure of which bears a striking resemblance to that of a malignant tumor. The fact that the proliferative capacity of the skin mole is sometimes exalted into malignant growth does not vitiate the contention that anaplastic cells may remain indefinitely at rest, since the tendency of the cutaneous mole is in the direction of quiescence, and malignant transformation occurs relatively rarely, and only in circumstances of irritation or injury.

On the other hand, certain cells possessing negligible histological indications of anaplasia are capable of diverting a considerable proportion of their energy to the process of growth, not only locally, but in situations removed from their place of nativity. Thus, chondromata may metastasize, and there is at least one case in the literature, sponsored by no less an authority than Orth,[2] of a metastasizing myofibroma of the uterus.

Interesting and important as these growths may be, both from an academic and practical stand-point, they are of negligible significance when compared with that larger category of neoplasms whose cells are frankly anaplastic and whose capacity to metastasize is exercised with such appalling freedom, namely, the carcinomata, sarcomata, and cognate growths. It is with this group that this paper deals, and I shall correlate the results of an analysis of 298 malignant tumors encountered among over 5000 autopsies at Bellevue Hospital with special reference to their metastases, the distribution of which often assumes great practical significance.

Incidence. Among 5155 autopsies at Bellevue Hospital in the past ten years there were 298 malignant tumors. Thus, 5.78 per cent. of all patients dying in Bellevue Hospital and coming to autopsy are subjects of malignancy. Of the 298 tumors, 264, or

¹ Rolleston and Jones: Lancet, June 2, 1906, p. 1527.
² Krische: Inaug. Dissert., Göttingen, 1889.

89 per cent., were of the epithelial or mesothelial variety, and 34, or 11 per cent., were sarcomata or endotheliomata. Therefore the proportion of epithelial to connective-tissue tumors in the series, as a whole, is 8 to 1.

Of the 298 tumors, 220, or 74 per cent., had gone to the stage of metastasis; in 19 instances, or 7 per cent., there was direct invasion of neighboring tissues without attendant metastases in remote parts, and in 59 cases, or 19 per cent., the growths remained localized as follows: Epithelioma of the urinary bladder 7, of the tongue 4, of the cheek and bronchus 1 each, of the esophagus 7; carcinoma of the stomach 10, of the sigmoid 6, of the cecum 5, of the uterus 3, of the rectum, pancreas, and liver 2 each, of the bile ducts and breast 1 each; sarcoma of the lung and osteosarcoma of the vertebræ 1 each, hypernephroma of the kidney 3, and of the adrenal 1.

The primary growths were distributed thus: epithelioma of the esophagus 23, of the urinary bladder 12, of the tongue 5, of the branchial clefts, bronchi, skin, and larynx 2 each, of the pharynx and penis 1 each; carcinoma of the stomach 84, of the gall-bladder 16, of the prostate 12, of the bile ducts 6, of the cecum 10, of the duodenum 3, of the pancreas 10, of the uterus 11, of a salivary gland and the jejunum 1 each, of unknown origin 2; hypernephroma of kidney 12, of adrenals 3; lymphosarcoma of the retroperitoneal nodes 4, of the anterior mediastinal nodes 3, of the posterior mediastinal nodes 2, of the cervical nodes 2, of the gastro-intestinal lymphoid structures 2, of general distribution 1; sarcoma of the breast 1, of the retroperitoneal nodes 2, of the periosteum 2, of the humerus, cervical nodes, sole of foot, thigh, mesenteric nodes, lung, and kidney 1 each; osteosarcoma of right leg, left leg, vertebræ 1 each; multiple myelogenous sarcoma 2, melanoma 1.

Of the 298 tumors the lymph nodes were metastasized 131 times, or in 44 per cent.; the liver 102, or in 34 per cent.; the pleura and lungs 73, or in 25 per cent.; the bones in 35, or 17 per cent.; the vertebræ, ribs, calvarium, sternum, femur, humerus, and pelvis being involved in the order named; the adrenals were metastasized 23 times, or in 8 per cent.; the kidney 17 times, or in 5.7 per cent.; the spleen 16 times, or in 5.3 per cent.; there was neoplasmic invasion of large veins in 13 cases, or in 4.7 per cent.; the pancreas was metastasized 13 times, or in 4.7 per cent.; the heart muscle 9 and the skeletal muscles 3 times, or in 4 per cent.; the ovary, mesentery, pericardium, and dura mater 7 times each, or in 2 per cent.; the small intestine, stomach, and scalp 3 times each, and the testicle and esophagus once each.

The figures just quoted show that as far as metastasis is concerned the organs of the body are divisible into a group the members of which are frequently the seat of metastasis, but in which primary growths are rare; a group composed of organs which are commonly the seat of primary growths, but which are rarely

metastasized; and a group the members of which are neither the
seat of frequent tumor growth nor of metastases.

THE ADRENALS. The adrenals were the seat of metastases in
23 instances, or in 8 per cent. The secondary growths were derived
from cancer of the stomach 5 times, the breast 4 times, the gall-
bladder and liver 2 each, the duodenum and splenic flexure 1 each,
from hypernephroma of the kidney once, and from sarcomata
6 times. Both adrenals were extensively metastasized 12 times
(52 per cent.), and of this number the glands were completely
destroyed in 8, or in 35 per cent. In addition to destruction of the
adrenal bodies by secondary growths, there were 3 cases of bilateral
adrenal hypernephromatosis attended by complete transformation
of the glands into tumor tissue. Thus, both adrenals were com-
pletely or almost completely destroyed in 15 cases, or in 65 per
cent. of the total number of neoplasmic lesions found in them, and
in not one of the number was pigmentation of the skin or mucous
membranes observed at autopsy, nor were these or other signs of
Addison's disease detected during life.

The suprarenal capsule represents, developmentally, two sets of
organs which, in higher forms, are fused, the cortex originating in
the mesoderm and the medulla in the neuro-ectoderm. It is not
astonishing, therefore, that pathologists have been able to differ-
entiate in man two genetically and clinically separable varieties of
neoplasm arising in the adrenal body, one of cortical and the other
of medullary origin. The adrenal hypernephroma, which is com-
posed of cells of cortical origin, is attended, in the young at all
events, by excessive bodily growth and precocious development of
the genitals and the secondary sexual characteristics.[3] These facts
harmonize with the generally accepted view that the adrenal cor-
tex is of companion origin with the testicle and ovary. On the
other hand, there is a familiar group of tumors of the kidney the
individual members of which are composed of cells morphologically
resembling, if not in distinguishable from, the cells of the suprarenal
cortex—the so-called renal hypernephromata. These tumors are
composed of cells which, according to one view, are derived from
nests of adrenal mesothelium aberrant in the renal cortex or other-
wise misplaced, as in the liver, according to another view, they
spring from adenomata of the convoluted tubules of the
kidney.[4]

The suprarenal tumor of medullary origin is the neuroblastoma,
and it arises from residual foci of embryonal nerve cells. Just as
the development of the adrenal cortex is in striking contrast to
that of the medulla, so is the neuroblastoma noticeably dissimilar
from the hypernephroma. Thus, it has been shown that the adrenal
medulla is an integral part of the chromaffin system and develops

[3] Bulloch and Sequeira: Tr. Path. Soc., London, 1905, lvi, 189.
[4] Alexander Fraser: Surg., Gynec. and Obst., June, 1916, p. 645.

in connection with the sympathetic. At a certain stage in its evolution there appear collections of so-called formative cells from which arises all that is cellular in the sympathetic system, including ganglion cells and the chromaffin constituents of the adrenal as well as of other localities. Termination of embryonal life does not necessarily denote completion of evolution in the adrenal medulla, but, on the contrary, the medulla is almost exclusively a product of postembryonal development, and up to, or even slightly beyond puberty, it contains collections of formative cells, or neuroblasts, constituting a source of potential tumor growth. Doubtless future investigation will show that aberrant formative nerve cells are of frequent occurrence elsewhere, that is to say, beyond the confines of the adrenal medulla, since isolated examples of neuroblastoma have been described in the cerebellum, at the root of the lung, in the soft tissues of the scapular region, and elsewhere.[5]

Thus far the neuroblastoma has been observed oftenest in children, in whom, it would appear, the growth is separable into two symptomatic groups, one attended by extensive metastases in the cranium and regional lymph nodes attended by secondary exophthalmus and ecchymosis of the lids, the other by rapidly increasing distension of the abdomen due to neoplasmic infiltration of the liver without ascites or jaundice.

Hypernephroma. Hypernephroma of the adrenal, as already indicated, occurring before the onset of puberty, brings about certain changes in bodily growth and in the development of the genitals and the secondary sexual characteristics. Developing after puberty, the lesion pursues the ordinary course of neoplasmic growth, and is marked by a palpable mass in the abdomen or even by visible enlargement corresponding to the location of the tumor, by irregular elevation of temperature due to absorption of the products of necrosis, and by pain. When the growth invades the pelvis of the kidney, as it not infrequently does, hematuria results, and may be constant or intermittent. In some cases the tumor grows slowly and remains localized, in which event operative removal may be followed by complete cure. In other instances the tumor grows with surprising rapidity, and not only attains enormous size, but infiltrates surrounding structures and gives rise to widespread metastases, particularly in the bones, lungs, and larger veins. In occasional cases signs of bone metastasis give the first indication of intra-abdominal growth, in other instances hemoptysis or hemorrhagic pleural effusion arising from intrathoracic metastases constitute the initial clinical disturbances.

In the Bellevue Hospital series of autopsies there were 15 cases of hypernephroma. Three arose in the adrenals, and all of them occurred in adults; 2 were bilateral. One was localized, and, of

[5] Douglas Symmers: Jour. Am. Med. Assn., 1913, lx, 337.

the other 2, one was accompanied by extensive metastases in the lungs, by a solitary metastasis in the scalp and liver, and by neoplasmic thrombosis of the inferior vena cava and both adrenal veins. In the remaining case the left adrenal measured 30 x 18 x 15 cm., and the right 15 x 8 cm., and there were numerous metastases in the pleura and lungs, in the retroperitoneal nodes, and a solitary metastasis in the heart.

Of the 12 cases of renal hypernephromata, the primary growth was in the left kidney in 7, and in the right in 5. The lower pole, contrary to the prevailing notion of the topographical origin of hypernephroma of the kidney, was the site of growth in 5 cases, the upper pole in 3, and in the other 4 cases the place was not recorded. Of the 15 cases metastases were present in the pleura and lungs in 9 (60 per cent.), and of these the peribronchial nodes were infiltrated in 4. The liver was extensively metastasized in 6 cases (40 per cent.), in 5 of which the pleura and lungs were also involved. Of the 15 cases the venous system was invaded seven times (46 per cent.), the inferior cava, renal, adrenal and iliac veins being chiefly concerned. Thus it appears that the hypernephroma exhibits little favoritism in the method of spreading its metastases, but embolizes the blood and lymph streams and infiltrates contiguous structures with scarcely discernible discrimination.

In 5 cases (33 per cent.) there were metastases to the bones, the vertebræ and ribs being oftenest affected.

THE VEINS. Neoplasmic invasion of the larger veins occurs occasionally, and is brought about primarily by direct extension and secondarily, by the lodgment of emboli. In the Bellevue Hospital series there was direct invasion of bloodvessels, with or without subsequent thrombosis, in 13 cases. Cancer of the gallbladder invaded the right renal vein once, in another case the right iliac vein was infiltrated, and in a third case there was neoplasmic thrombosis of the portal vein giving rise to blood-stained ascites. A case of medullary carcinoma of the stomach was attended by neoplasmic thrombosis of the splenic vein followed by numerous small metastases in the spleen due to retrograde embolism. In another case of gastric cancer there was neoplasmic thrombosis of the left iliac vein. In still another case neoplasmic thrombosis of the portal vein was associated with an enormous sarcoma of the pancreas. The remaining 7 cases (46 per cent.) of neoplasmic invasion of bloodvessels were directly traceable to renal or adrenal hypernephromata.

OVARIES. The ovary was metastasized in only 5 cases—4 times in primary cancer of the stomach and once in a cancer of the breast. The right ovary was alone involved in 3 cases, the left in 1, and in 1 case both ovaries were infiltrated.

There is a metastatic neoplasm of the ovary, however, which would appear to deserve rather more detailed consideration, namely, the

one described by Krukenberg[6] in 1896. This investigator, working in Marchand's laboratory, observed 6 examples of a malignant tumor which he believed to be of ovarian derivation and which is composed of a stroma richly infiltrated by large, mucus-bearing cells counterfeiting the shape of a signet ring. He was unable, however, to determine the origin of the cellular unit, and was consequently at a loss for a descriptive designation of the growth as a whole, but finally gave it the ponderous and rather equivocal title of "fibrosarcoma mucocellulare ovarii (carcinomatoides)." Since the appearance of Krukenberg's paper other observers have noted a growth in the stomach wall of identical histology, and have advanced the view that the tumor is primarily gastric and that the ovarian changes are metastatic.

The so-called Krukenberg tumor appears to be little known in this country. In fact, I know of but one case a description of which appears in the English language (Outerbridge[7]) and there is no acceptable portrayal of the subject in any of the English or American text-books with which I am familiar. Three cases have come to my notice in New York City in the past ten years—2 occurring in the surgical service of the New York Hospital and 1 at Bellevue Hospital. It was not practicable to investigate the New York Hospital cases beyond the field opened by surgical interference. Suffice it to say that in both cases the ovaries were regarded as primarily involved and were removed. The Bellevue Hospital case was made the subject of thorough postmortem investigation, and is as follows:

The patient, N. D., aged thirty-two years, married, was admitted in the twentieth week of pregnancy. For five months previous to admission she had been mentally dull and for some time had suffered severe attacks of vomiting. Two weeks before admission vomiting became incessant and was accompanied by epigastric pain. She had lost greatly in weight.

Autopsy. Throughout the parietal peritoneum were numerous flat, firm, whitish plaques from 1 to 2 mm. in diameter. The left ovary was sclerotic and cystic, but showed no naked-eye indications of infiltration. The right ovary measured 6 x 4 cm. and was nodular. The pyloric region of the stomach presented a firm, grayish mass which extended along the lesser curvature for a distance of several centimeters. The regional lymph nodes were infiltrated and there were a number of nodules embedded in the mesentery of the large intestine.

Microscopic examination of the right ovary, stomach, and peritoneal metastases showed the presence of infiltrating cells identical with those described by Krukenberg—that is to say, large cells with sickle-shaped nuclei peripherally placed, a relatively small

[6] Arch. f. Gynäk., 1896, p. 287.   [7] Am. Jour. Obst., 1911, lxiv.

amount of pinkish staining cytoplasm, and a larger amount of cytoplasm composed of granules staining reddish violet with weak aqueous thionin. According to unpublished work by M. E. Hall in the laboratories at Bellevue Hospital the characteristic cells of the Krukenberg tumor are derived from the parietal cells of the fundus glands in the mucosa of the stomach. From a study of Hall's preparations and the microscopic sections of the two tumors encountered by myself at the New York Hospital, I am strongly inclined to accept this view as the most satisfactory of the several that have been presented.

KIDNEYS. The kidney was metastasized seventeen times (7 per cent.). The metastases were derived from sarcomata eight times (47 per cent.), and from gastric, duodenal, and breast carcinomata seven times (43 per cent.), from an adrenal hypernephroma once, and from an hypernephroma of the opposite kidney once. Both kidneys were involved in 8 cases, the right was alone involved five times and the left four times.

SPLEEN. In 298 malignant tumors the splenic pulp was metastasized sixteen times, or in 5.3 per cent. Of the 16 cases, 14 were tumors of epithelial origin and the remaining 2 were sarcomata. The preponderance of epithelial tumors, however, is apparent rather than real, for the proportion of 7 to 1, which obtains for the series as a while, is likewise applicable to the metastases in the spleen.

Not only are splenic metastases of rare occurrence, but they are practically always small in both size and number, seldom growing beyond 1 cm. in diameter and rarely exceeding a half dozen. In but one of the Bellevue Hospital autopsies was an exception found, and in that case the spleen was riddled by small metastatic deposits following neoplasmic thrombosis of the splenic vein occurring in association with a medullary cancer of the stomach. Moreover, in every one of the 16 cases there were numerous metastases in other organs, notably the liver, lymph nodes, one or both adrenals, the bone marrow, peritoneum, omentum and mesentery.

In 7 cases the metastases in the spleen were derived from carcinomata of the stomach (43.7 per cent.), in 3 cases the primary growth was in the breast (19 per cent.), in 1 case there was a primary hypernephroma of the kidney, in 1 case a primary carcinoma of the liver, in 1 case the cecum was the point of origin and in 1 case the jejunum.

BONY SYSTEM. From the stand-point of metastasis the tumors of the osseous system are divisible into three groups. One includes those tumors which appear to have multiple points of origin within the osseous system itself, and which may or may not erode the cancellous bone and bring about infiltration of neighboring structures, but in which metastasis is practically unknown. This group includes the multiple myelomata,[8] the multiple primary giant and

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[8] Vance: AM. JOUR. MED. SC., November, 1916, p. 693.

spindle cell growths described by Barry[9] and by Martland,[10] and the multiple primary intravascular hemangio-endotheliomata recently described by Symmers and Vance.[11]

The second group includes the spindle and giant-cell sarcomata, and other varieties of connective-tissue growth in which metastasis may occur in other parts of the bony system as well as in the soft tissues and viscera.

The third group embraces those tumors whose metastases display a distinct predilection for the osseous system, bringing about two widely remote series of changes—one characterized by osteosclerosis, as typefied by the growth of certain metastases of prostatic origin, and the other by destructive changes in the bones due to deposits from such tumors as cancer of the breast, thyroid, and stomach and the hypernephromata.

Bone Metastases. Bone metastases may be single or multiple, visible or palpable, or so successfully concealed that they may not be detected even at autopsy, or they may be suddenly revealed by spontaneous fracture of an extremity ensuing upon trivial cause, or by sudden or gradual development of symptoms referable to pressure upon the spinal cord following displacement of the vertebræ. In one of the Bellevue Hospital autopsies the patient complained during life of hoarseness and of excrutiating pain on swallowing. He suddenly developed paresis of both lower extremities, attended by disturbances in sensation and urinary symptoms. The knee-jerks were not obtainable. At autopsy there was a tumor in the upper portion of the esophagus lying directly under an intact mucous membrane. The bodies of the lowermost cervical vertebræ were infiltrated and displaced, producing pressure upon the cord. Microscopic examination of the growth in the esophagus revealed an adenocarcinoma derived from an aberrant salivary gland with structurally identical metastases in the spinal column.

In still another type of case the symptoms of bone metastasis are essentially those of pressure on the sensory nerve roots.[12]

Another and not uncommon variety of bone metastasis is solitary, and surgical removal of the secondary growth sometimes appears to be not only justifiable but imperative, particularly when the primary growth is accessible, as in cancer of the thyroid, the majority of whose metastases are single, grow slowly, and are often so situated as to invite removal, *e. g.*, in the lower jaw, humerus, femur, and sternum. Whether the thyroid itself should be removed is a question demanding the highest surgical judgment. Thus, in the case of a woman, aged forty-two years, who suffered a fracture of the humerus from a trivial cause, a quantity of softened and hemorrhagic tissue

[9] Quoted by Martland, loc. cit.
[10] Proc. New York Path. Soc., 1915, xv, 119.
[11] Am. Jour. Med. Sc., 1916, xlii, 28.
[12] Blumer: Yale Med. Jour., 1911, xviii, 153.

was curetted from the site of injury by Dr. George D. Stewart,
perfect bony union resulted, and the patient remains well four
years later. There was no detectable growth in the thyroid itself.
Microscopic examination of the material curetted from the humerus
showed a richly vascular tumor, the unit of which was an acinus
structurally identical with that of the thyroid gland. The question
naturally arose as to whether the bone lesion represented prolifera-
tion of thyroid tissue aberrant in the humerus or whether it was a
metastatic growth from a clinically indetectable thyroid tumor.
Rests of thyroid tissue in the bones have not, as far as I know, been
described, and their presence in that situation is entirely pre-
sumptive. On the other hand, cases are by no means unknown in
which bone metastasis with removal of the thyroid has failed to
show neoplasmic growth in the latter, and, conversely, minute
thyroid tumors have been known to occasion innumerable secondary
growths in the osseous system and elsewhere.

In other circumstances the thyroid carcinomata are not bene-
ficently inclined. In the case of a woman, aged fifty-eight years,
who complained of right-sided hemicrania of four weeks' duration,
percussion showed tenderness over the anterior portion of the right
parietal region, and the thyroid was slightly enlarged and nodular.
Dr. Van Horn Norrie made the diagnosis of cancer of the thyroid
with metastases in the skull. Two weeks later the patient developed
a mass corresponding to the area of tenderness in the parietal region.
The mass grew rapidly. Autopsy revealed a carcinoma of the
thyroid with infiltration and destruction of the right parietal and
adjacent temporal bone, two small nodules in the liver, numerous
metastases in the lungs, and a solitary nodule in the right supra-
clavicular fossa.

In the Bellevue Hospital autopsies the marrow of one or more
bones was metastasized in 35 cases, or 11 per cent. The primary
growths were as follows: carcinoma of the prostate 2, breast 10,
stomach 6, thyroid 2, tail of pancreas 2, cancer of an aberrant
salivary gland and of the jejunum 1 each, hypernephroma of the
kidney 6, spindle-cell sarcoma 3, melanoma 1, and myelogenous
sarcoma 1.

The vertebral column was involved twenty-five times. In the
metastases from the prostatic growths the bones showed sclerotic
changes, while in the breast, stomach, and other tumors the lesions
in the bones, with a single exception, were destructive, in several
instances permitting spontaneous fracture of the extremities or
displacement of the vertebræ, with pressure upon the cord. The
ribs were metastasized sixteen times, and in 8 of these there were
companion lesions in the vertebræ. The bones of the skull were
metastasized nine times, the sternum four times, the femur and
pelvic bones three times each, and the humerus twice.

ESOPHAGUS. There were 23 cases of epithelioma of the esophagus, and in 9 of them the liver was metastasized—three times in association with growth in the upper end, three times in the middle, and three times in the lower portion. It is interesting to observe that in all 3 cases of epithelioma of the upper end of the esophagus the metastases in the liver were large and numerous. In 1 case the liver weighed 5680 gm., and in another 8449 gm. In the remaining 6 cases the secondary growths in the liver were either solitary or limited in number and size.

The perigastric lymph nodes were infiltrated in 10 cases, the periesophageal nodes nine times, the lungs and pleura seven times, the mediastinal nodes three times, the cervical nodes twice, and the heart once. The thyroid was twice invaded by direct extension, and the walls of the aorta, a bronchus, and the trachea once each.

STOMACH. From the stand-point of the pathologist the two outstanding varieties of carcinoma of the stomach are the medullary adenocarcinoma, springing from fully developed gastric tubules, and the adenocarcinoma arising on the basis of newly formed or regenerated tubules in the immediate vicinity of an old peptic ulcer. As far as their metastases are concerned there are certain differences between the two which are not without practical significance.

In the Bellevue Hospital series of autopsies there were 46 examples of medullary cancer of the stomach. Eight, or 18 per cent., were not accompanied by metastases, although the primary growths involved an extensive sweep of the stomach wall. In 1 case there was a solitary metastasis in the liver, in 15 cases, or 33 per cent., there were a few small metastatic deposits in the liver, in 3 cases the liver was the seat of numerous metastases, and in 19 cases or 41 per cent., the liver was free.

There were 22 instances of carcinoma of the stomach associated with preëxisting ulcer, and in 10, or 46 per cent., the liver was greatly enlarged and riddled with metastases, in 1 case it was the seat of a large solitary metastasis, in 9 cases, or 40 per cent., there were no metastases in the liver, and in 2 cases the growth was confined to the stomach. In all of the cases the primary growth was small, rarely exceeding a few centimeters in diameter. In other words a carcinomatous lesion of the stomach growing on the basis of an old ulcer may be insignificant in size and yet give rise to numerous and extensive metastases, particularly in the liver—an argument in favor of early eradication of the so-called healed ulcer with its circumferential zone of regenerated and immature epithelial tubules.

INTESTINES. There were 32 examples of carcinoma of the intestines as follow: duodenum 3, jejunum 1, cecum 10, ascending colon 2, splenic flexure 3, sigmoid 6, rectum 7.

The duodenal cancers were all formed on the basis of healed ulcers, and all of them were attended by extensive metastases, particularly in the liver and regional lymph nodes. In one of the cases the skin, pancreas, rectus muscle, thyroid, trachea, heart, liver, adrenals, kidneys, and dura were metastasized, which is not only an extensive but an unusual distribution. The case of carcinoma of the jejunum was likewise founded on the basis of a healed ulcer, and gave rise to extensive metastases in the pleura, lungs, mediastinal, mesenteric and thoracic and cervical nodes, and in the liver and vertebræ.

Of the 10 carcinomata of the cecum 5 were unattended by metastases, in 2 cases the pericecal nodes were alone metastasized, and in 3 cases infiltration of the pericecal nodes was associated with secondary nodules in distant parts.

Of the 5 colon carcinomata 2 were free from metastases, and 3 were associated with fairly extensive involvement of the regional nodes and of distant organs.

Of the 13 cases of carcinoma of the sigmoid and rectum, 8 were unattended by metastases, and 5 were associated with involvement of the regional nodes and distant organs.

Of the 28 cancers of the lower intestinal tract 15, or 53.5 per cent., were unattended by secondary growths. This is in striking contrast to the high degree of malignancy displayed by tumors of the stomach and of the upper intestinal tract.

CARDIAC AND SKELETAL MUSCLE. There were 12 cases of muscle involvement. In 9 instances the heart muscle was affected and in 3 the skeletal muscles. In 3 of the cardiac cases direct infiltration arose from mediastinal lymphosarcomata and nodular metastases occurred 5 times—1 from a cancer of the duodenum, 1 from a spindle cell sarcoma of the humerus, 1 from an epithelioma of the esophagus, 1 from an adrenal hypernephroma, and 1 in a case of melanomatosis.

The skeletal muscles showed nodular metastases three times only. There was a small solitary metastasis in the right rectus derived from a cancer of the duodenum, a single nodule in the right deltoid from a spindle-cell sarcoma of the sole of the foot, and several small nodules in the diaphragm from a primary cancer of the liver.

THYROID. There were 12 cases of metastatic involvement of the thyroid gland. In 3 instances there was direct extension from primary esophageal growths, and in 2 cases the thyroid metastases were but the local expression of tumor dissemination. Of the remaining 7 cases the secondary growths in the thyroid were nodular in character, and were derived from carcinoma of the duodenum, breast, and stomach once each, and from hypernephroma and sarcoma twice each.

SKIN, SUBCUTANEOUS TISSUES, AND LYMPH NODES. Enlargement of the superficial lymph nodes often occurs in association with

malignant growths, and the question then arises as to whether the secondary process is metastatic or due to lymphoid hyperplasia dependent upon absorption from ulcerative areas, or upon reactive hyperplasia of the endothelial cells of the lymph sinuses. In any event, determination of the nature of the secondary process is of importance from the stand-point of both prognosis and treatment. In the same way histological investigation of secondary enlargements in the skin or superficial nodes is occasionally of great assistance in determining not only the nature and sometimes the location of deep-seated growths, but the method of treatment. Thus, in a case which came under my observation at the New York Hospital some years ago a solitary nodule removed from the region of the scapula revealed a new growth which strongly suggested metastasis from an adenocarcinoma of the stomach, and the institution of palliative operative procedures based on this finding confirmed the suspicion. In another case, in the same hospital, removal of a small nodule from the head of the fibula resulted in the discovery of a hypernephroma of the kidney.

In the Bellevue Hospital series there were 11 cases, or 3.7 per cent., in which enlargement of superficial structures depended upon metastasis from deep-seated growths. In a case of cancer of the duodenum there were several small nodules in the skin of the abdomen, back, shoulders, and scalp; there were 3 cases of enlargement of a solitary supraclavicular node in association with deep visceral cancers, and 2 instances of axillary involvement, in a case of hypernephroma of the kidney there was a small nodule in the skin of the chest, and, in a second case, a nodule beneath the scalp, and in 2 cases of epithelioma of the upper end of the esophagus there were nodules in the cervical region.

In still another case there were innumerable nodules in the skin, and microscopic examination of one of them during life showed histological changes scarcely to be differentiated from those of a neurofibroma. At autopsy, however, a small scirrhous cancer of the stomach was found, and examination of numbers of skin nodules from various parts revealed localized areas of sclerosis in the subcutaneous connective-tissue embedded in which were minute alveoli of cancer cells representing metastases from the growth in the stomach. In view of the histological changes observed in the skin during the life of the patient, and because of the number and distribution of the nodules and their painful nature, the case was regarded clinically as an example of von Recklinghausen's disease (neurofibromatosis universalis).

SUMMARY AND CONCLUSIONS.   1. Slightly less than 6 per cent. of all patients dying in Bellevue Hospital and coming to autopsy are subjects of malignant disease.

2. Of 298 malignant tumors observed postmortem at Bellevue Hospital, 220, or 74 per cent., were attended by metastases. The

lymph nodes, liver, pleura and lungs, bones, and adrenals were the organs most commonly metastasized, and they were involved in the order named.

3. Epithelial tumors predominated over those of connective-tissue origin in the proportion of 8 to 1.

4. As far as the process of metastasis is concerned, the organs of the body are divisible into 3 groups: (1) A group made up of organs which are frequently the seat of metastasis, but in which primary growths are exceedingly rare; (2) a group composed of organs which are more or less commonly the seat of primary growths, but which are themselves rarely metastasized. For example, the lymph nodes, liver, lungs, pleura, and bone marrow give rise to malignant growths only rarely, but metastasis to these organs is common, while the stomach, breast, pancreas, prostate, etc., frequently give rise to malignant tumors, but are themselves seldom metastasized. Finally there is a third group of organs the members of which are neither the seat of frequent tumor growth nor of metastasis, namely, the spleen, heart and skeletal muscle, kidney, thyroid, etc.

(a) Splenic metastases are of rare occurrence and are practically always small in both size and number. They are frequently associated with numerous metastases in other situations. From this it seems reasonable to infer that metastasis of the spleen is late in point of time and that it follows only after frequent and persistent visitation of tumor cells to the splenic sinuses. Further evidence that the spleen is antagonistic to the growth of metastatic deposit is afforded by the fact that in 3 cases of carcinomatosis and in one of melanomastosis the spleen was free from detectable sign of involvement, although, in company with every other organ in the body, it must have received an abundance of cells whose vegetative capacity was in no wise different from those delivered to and successfully inoculated in other parts. The conclusion, it seems to me, is justifiable that the inimical attitude of the spleen toward the growth of metastases is dependent upon resistence inherent in the splenic cells, reënforced, perhaps, by lytic properties in the blood of the splenic sinuses. No doubt the same argument is applicable to other organs in which metastases are infrequent and small, notably, the kidneys, thyroid and muscles.

(b) Metastatic involvement of muscle tissue is a rare event. A new growth may abut directly on the muscle and destroy it as a result of pressure, but infiltration of tumor cells between muscle fibers is not common, and nodular metastasis is almost unknown. On the other hand the movement of tumor emboli along the intramuscular lymphatics is frequent enough, and their passage is probably facilitated by mechanical conditions, although there are many muscles whose activity is reduced to a minimum in cachectic subjects—in fact, conditions in them are equivalent to rest, and yet metastasis is almost unknown. Whether there is a

substance produced by the muscle itself that serves as an additional obstacle to the deposition and growth of tumor cells is a question.

(c) The kidney, although seldom metastasized, appears, relatively speaking, to be a favorite seat for the lodgment of metastases from sarcomata. Carcinomatous metastases in the kidney are rare and are small in size and number, seldom exceeding a few millimeters in diameter nor more than a half-dozen, and are practically always found in the cortex.

5. The great majority of all splenic metastases are derived from tumors which are notorious for metastasizing to bone marrow—cancers of the stomach and breast, and hypernephromata—a fact which assumes additional interest when it is recalled that there is a structural resemblance between bone marrow and the splenic pulp.

6. Both adrenals were completely or almost completely destroyed in 65 per cent. of the total number of neoplasmic lesions observed in them. In not one of the number was pigmentation of the skin or mucous membranes observed at autopsy, nor were these or other signs of Addison's disease detected during life.

(a) The suprarenal capsule, like the kidney, is a favorite site for the lodgment and growth of sarcomatous metastases, the proportion of epithelial to connective-tissue metastases being only 3 to 1.

7. Neoplasmic invasion of the larger veins, with or without subsequent thrombosis, is uncommon, and occurred only thirteen times, or in 4 per cent., of the Bellevue Hospital series. The hypernephroma shows the greatest avidity for the vessels, 7 out of 15 cases, or 46 per cent., having produced secondary lesions in the veins. Suspicion should be directed to neoplasmic thrombosis of the portal vein in rapidly developing ascites, and to similar changes in the common iliac vein in edema of the lower extremity, when the physical signs in question are otherwise inexplicable.

8. The so-called Krukenberg tumor is not primary in the ovary, but in the stomach, where it springs, most likely, from the parietal cells of the fundus glands (Hall, Symmers). The ovarian manifestations are purely metastatic, and are apt to be bilateral.

9. Cancer of the stomach, occurring on the basis of regenerated epithelial tubules at the periphery of an old peptic ulcer, may be insignificant in size and yet give rise to innumerable and widespread metastases, whereas the medullary cancer, which appears to spring from mature gastric tubules, is apt to attain enormous dimensions, showing, at the same time, a noticeable tendency to remain confined to the stomach. In fact, it seems probable as a general proposition, that adenocarcinomata that arise on the basis of regenerated epithelial structures, such as are constantly seen around old gastric ulcers and in chronic hyperplastic gastritis, metastasize earlier and more extensively than those which spring from an apparently normal mucosa. Thus, the adenocarcinomata of the breast occurring in associa-

tion with chronic productive mastitis and attended by compensatory regeneration of epithelial acini, and those cases which follow lactation hyperplasia, are among the most malignant of all known varieties of cancer of the breast. The adenocarcinomata of the gallbladder associated with regenerative efforts on the part of the mucosa to repair lesions mechanically produced by gall-stones, are exceedingly malignant, and give rise to extensive metastases and to early involvement of contiguous structures. Carcinoma of the prostate is practically always associated with histological changes indicating neoplasmic transformation of regenerated epithelial tubules occurring in association with chronic interstitial prostatitis, and the same is true of carcinoma arising on the basis of adenomatoid hyperplasia of liver cells in cirrhosis. On the other hand, carcinoma springing from apparently mature tubules, or in situations where cells are protected from injury, are apparently less active in the matter of producing secondary growths. The explanation, I think, lies partly in the fact that regenerated tubules often approach the fetal type of architecture, and in them the function of growth is a prominent if not a dominant feature, whereas tumors springing from apparently mature epithelium are composed of cells not so markedly consecrated to assimilation and reproduction, such, for example, as the colloid-producing cancers of the thyroid, the milk-producing cancers of the breast, etc.

10. Of 28 cancers of the lower intestinal tract, 15, or 53.5 per cent., were not accompanied by infiltration of surrounding structures or by metastasis. This is in striking contrast to the high degree of malignancy shown by tumors of the stomach and upper intestine.

I wish to acknowledge, with thanks, assistance rendered by Dr. E. E. Stern, of the interne staff of Bellevue Hospital.

THE DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL CONDITIONS.

By A. McNiel Blair, M.D.,

SOUTHERN PINES, N. C.

ANATOMICALLY the mediastinum is divided into an anterior position lying in front of the roots of the lungs and a posterior position behind them, the two being continuous; but since the use of the roentgen-rays and perfected fluoroscopic examinations (by placing the patient in a right oblique anteroposterior position), clinically three distinct mediastinal spaces are made apparent, and are called the anterior, medial, and posterior.

The anterior mediastinal space contains the lymph nodes, the areolar tissue, and the thymus or its remains. The medial and

posterior contain the heart with its afferent and efferent vessels, the trachea, the bronchi, the esophagus, thoracic duct, vagus, phrenic and sympathetic nerves, and lymph nodes.

As thoracic aneurysm is frequently the cause of sudden death referred without autopsy to other causes, and is more common than was once supposed, the condition being so often overlooked, I will dwell more especially upon thoracic aneurysm, using it as a working basis from which the differential points of diagnosis of mediastinal conditions generally may the better be brought out, in view of the common symptomatology of mediastinal conditions in general.

When the walls of an artery become diseased singly or *en masse,* with a resulting dilatation, we have a condition called aneurysm; therefore a true aneurysm represents a more or less localized dilatation of an artery, due to the weakening effect of a chronic degenerative arteritis, syphilis standing first as the cause of a large majority of the cases.

Intemperance in eating and drinking, physical and mental overwork or overstrain may act as contributory causes, the first symptoms often arising after severe or prolonged muscular effort. Some authors describe "dating of symptoms" from trauma, such as severe falls or railroad accidents. It is not improbable, however, that a congenital weakness of the vessels existed primarily, due to inherited process, traceable to one of the factors before mentioned.

Greene states: "Roughly speaking, three-fourths of all aneurysms are aortic; nineteen-twentieths of these are found in the thoracic aorta; of these 90 per cent. are sacular; from 80 per cent. to 90 per cent. occur in the male, and 50 per cent. occur between the ages of thirty-five and fifty." The chief points of attack are the root of the aorta, the junction of the ascending and transverse portions, and the descending arch, in the order indicated.

First let us consider the anatomical arrangement. The arch consists of three portions: the ascending, the transverse, and the descending. The ascending lies behind the pulmonary artery, at the level of the third costal cartilage, being separated from the sternum by the pericardium only, which covers it for about 5 cm.; therefore, aneurysms existing in the ascending portion may rupture into the pericardial cavity.

The transverse portion of the arch passes from a point corresponding to the first right interspace, directly backward into the mediastinum, to the left of the vertebral column, giving off three branches: the innominate, the left common carotid, and the subclavian arteries.

The descending or thoracic aorta begins at the third dorsal vertebra and passes along the median line to the aortic opening in the diaphragm.

Look for a moment at the cross-section of the chest and consider "that a transverse line touching the anterior surface of the bodies of the dorsal vertebra lies about the middle of the anteroposterior

diameter of the thorax," and as the symptoms are dependent upon size, site, and direction of the growth of the aneurysm, the condition may remain latent even with large dilatation, or may be manifested by distinct pressure effects, with or without external physical signs. It may grow forward to the sternum, eroding the latter, appearing as a pulsating tumor just at the manubrium or to the left of it.

"The arch being in close contact behind, with the trachea, esophagus, thoracic duct, and left recurrent nerve, which winds around it; all these may be compressed by the growth or it may burst into the trachea or esophagus, causing fatal hemorrhage."

The orifice of one of the large branches may be closed by atheromatous changes, causing a disappearance or delay in the radial pulse on the corresponding side. This brings us to the old classification: (a) aneurysms with signs but no symptoms; (b) aneurysms with symptoms but no signs; (c) aneurysms with neither symptoms nor signs.

The so-called classical symptoms, we are told, develop only in certain cases, usually when terminal stages have been reached, and in these cases the diagnosis is comparatively easy. But what about the remainder of these cases, in which wrong diagnoses simply permit of the further shortening of the already shortened term of life allotted to this class of sufferers?

The usual symptoms complained of by the patient are pain, precordial oppression, difficulty in breathing, and feelings of general weakness, along with one or more of the predominant pressure phenomena.

Behan, in his book on *Pain*, in speaking of the pain in aneurysm, describes it as constant and gnawing, as a rule. In some cases it is paroxysmal, though often in the early stages it may be entirely absent. In many cases the patient locates the pain over the tumor mass by pressing over the affected area with his hand. A characteristic of the disease is that deep pressure is always grateful.

The pain above described as gnawing, boring, etc., is caused by pressure upon the chest wall, while upon the sensory nerves the pain is referred to their peripheral distributions. These referred pains vary with the situation of the tumor.

Aneurysms of the thoracic aorta, however, do not produce so much pain as do those of the abdominal aorta. In all cases of suspected aneurysm, careful inquiry should be made as to the presence of pain, because the patient frequently neglects to mention it.

The pressure phenomena have been ingeniously classified as follows:

1. Pressure upon the esophagus results in dysphagia.

2. Upon the trachea, pressure causes the brazen cough (gander cough), also dyspnea, stridor, bronchorrhea, and hemoptysis even without rupture of aneurysmal sac.

3. Upon the root of the lung and pleura, pressure leads to deficient

lung aëration, with symptoms suggesting phthisis and pulmonary collapse, *e. g.*, case cited by Dr. John Pryor, during his service with Professor Koch. The patient responded to tuberculin reaction, but died ten days later, and autopsy showed a ruptured aneurysmal sac.

4. Pressure upon the nerve trunks results in the neuralgic type of pain, being paroxysmal and intermittent.

Fig. 1.—Aortic aneurysm. Mr. G., aged thirty-six years. Luetic history positive. Blood-pressure reading: right, 125–110; left, 115–95. Characteristic physical signs but no symptoms.

Fig. 2.—Aortic aneurysm. Mr. C. P. Y., aged fifty years. Luetic history positive. Blood-pressure: right, 125–90; left, 110–60. No characteristic physical signs, except delayed left radial pulse. Expiratory type of dyspnea, with excessive localized sweating. (Negative is shown reversed.)

A point of difference in the pain of aneurysm and aortitis is exemplified in Figs. 3 and 4. In this particular patient the pain was localized at the right of the third costal cartilage and over the middle portion of the manubrium, and was referred to the back of the

neck and over the shoulders, shooting to the back of the head.   It
differed from the description of aneurysmal pain, in that it was
sudden in its onset, occurred often in the epigastrium, and resembled
angina pectoris in severity and suddenness.   Paroxysms lasting only

Fig. 3.—Miss McC., aged sixty-three years.   Blood-pressure, 150–125.   (See text.)
In this case anginal type of pain experienced, with unusual distribution, and empha-
sizes Behan's description of difference in the type of pain in aortitis from that of
true aneurysm.   Patient died suddenly, during apparent convalescence, from lobar
pneumonia.

Fig. 4.—Miss McC., aged sixty-three years.   Abdominal findings in Fig. 3, with
aortitis and aortic dilatation.

a few minutes were often produced by exercise and ingestion of food,
and elevation of arterial pressure when accompanied by contraction
of the peripheral superficial vessels.

5. Pressure upon the pulmonary artery gives a systolic murmur, due to primary hypertrophy of the right ventricle, with subsequent dilatation of right ventricle.

6. From the sympathetic pressure we have dilated or contracted pupils, unilateral sweating, or pallor.

7. From pressure on the cardiac plexus, the anginal attacks.

8. While edema of the upper extremity and cyanosis come from the superior vena cava pressure.

9. Loss of flesh usually occurring in these cases, the resulting marasmus might readily be traceable, in part, to pressure upon the thoracic duct.

10. While the vagus interference could result in dyspepsia, nausea, vomiting, dyspnea, and hiccough.

11. Unilateral paralysis results from the phrenic pressure.

12. While hoarseness, aphonia, spasm or paralysis of the left vocal cord and paroxysmal dyspnea come from pressure on the recurrent laryngeal nerve. This classification of pressure symptoms applies to mediastinal growths in general, including aneurysms.

It is hardly necessary to go over the physical signs in detail; I wish only to touch upon certain points.

Inspection is very important. The manubrium and the back, between the left scapula and the spine, should come in for special scrutiny.

A visible tumor, yielding expansile pulsation, is rarely met with. The peripheral signs of associated aortic regurgitation may be present. Cardiac hypertrophy, as indicated by the apex beat, is commonly but not invariably associated. Atheromatous changes in peripheral vessels; cyanosis, localized edema; unequal pupils, vasomotor symptoms, stridor, visible dyspnea; paralysis of the vocal cords associated with hoarseness or aphonia; and brazen cough are all recognized by aid of inspection.

In palpation one seeks to elicit the expansile pulsation and thrill and the so-called diastolic shock.

Tracheal tugging, described by Oliver, has been met with in so many cases other than aneurysm, and has been absent when aneurysm actually existed, that it is not so important as we were once taught, for example, in a case of adhesions of the left pleura (Fig. 5) this physical sign was in evidence. The palpation of the radial pulses and carotids, for comparison, is very important.

In aneurysm of the ascending portion of the arch involving the innominate the right radial and carotid are affected; in the descending portion, the left radial. A delayed pulse may accompany aneurysm of the transverse portion.

As to percussion, auscultatory percussion is by far the more reliable, and may be further checked by use of the tuning fork, as auscultatory findings are not constant factors, owing to coexisting or associated valvular disease. One can hear at times a systolic

bruit, often harsh, vibrant, and associated with palpable thrill, coming from or produced by the sac itself.

A localized systolic murmur heard at the left back is given as an important sign. A distinct ringing metallic second sound heard, not over the aortic valve itself, but over the sac, is given by Greene as a
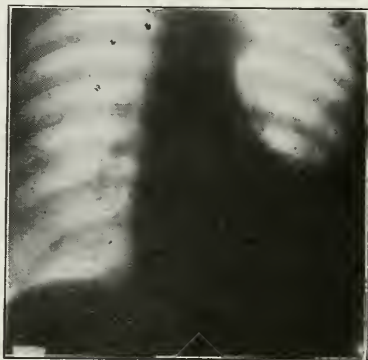

Fig. 5.—Mrs. J. L. R., aged fifty years. Negative Wassermann. Marked cardiovascular symptoms. Blood-pressure, 164–140. Tracheal tug. Present condition shown to be due to left pleural adhesions and thickening, with mechanical traction accounting for aortal symptoms.

Fig. 6.—Miss L., aged twenty-one years. Tuberculosis of bronchial glands only; showing type of mediastinal infiltration in this class of cases.

most important sign. It should be added that much is to be learned from systematic blood-pressure readings, not from one arm only but from both, and compared. The systolic as well as the diastolic readings are necessary, as the variation of the pulse-pressure on the two sides is most important. And last, but not least, often the fluoro-

scopic and roentgen-ray examination offer the only means of an early diagnosis at our command.

DIFFERENTIAL DIAGNOSIS.   Mediastinal abscess is differentiated by its rapid development with symptoms of suppuration, and absence of aneurysmal symptoms other than those from pressure.

FIG. 7.—Dr. J. W. B., aged forty-seven years.   Sarcoma of the mediastinum; left-sided glandular involvement of the sublingual, submaxillary and cervical glands, along with tongue involvement.   Case strongly resembled Hodgkin's disease. (Negative is shown reversed)
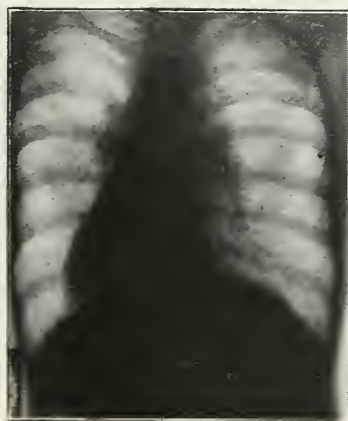
FIG. 8.—Miss E. M. E., aged forty-five years.   Blood-pressure, 145-110.   Bronchial asthmatic dyspnea included because of cardiovascular symptoms in the case. Bronchial glands, with dilatation of the bronchi contributory factors.

Pulmonary fibrosis, or any case involving the retraction of the lung, may give rise to suggestive pulsation in aneurysmal areas; but ordinary methods reinforced by fluoroscopic examination of the arch will exclude this condition.

Pulmonary tuberculosis, with large cavity, adjacent to aneurysmal areas, may produce pulsation and certain aneurysmal signs, but history, sputa, breath sounds, etc., should prevent error.

Anemic pulsations can be readily differentiated.

Fig. 9.—Mr. L. P. S., aged sixty-three years.   Cardiac hypertrophy and aortic dilatation chronic.   Symptoms of decompensation; no pain; dyspnea marked; gastrointestinal disturbance.   Sudden death.
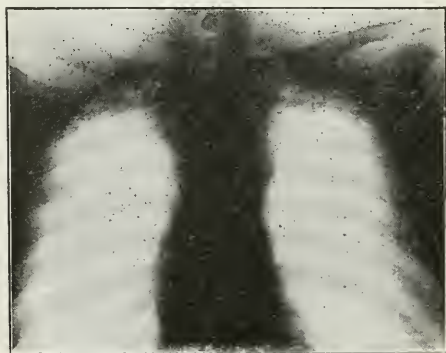
Fig. 10.—Mr. W. J., aged seventy-one years.   Senile aortic dilatation presenting itself in the course of cardiac hypertrophy associated with interstitial nephritis.

Malignant growths in the mediastinum are best differentiated by means of the roentgen-rays.   In their absence, knowledge of primary focus of malignant growth, absence of auscultatory signs of aneurysm, rapid emaciation, absence of expansile pulsation should be of material help in differentiation.

The coexistence of the two conditions, malignant growth and aneurysm, have been reported.

Growths of the mediastinum may call for differentiation. Good-kind speaks especially of those which may originate:

(1) Primarily from structures within the mediastinum; (2) from contiguous organs, growth of which may encroach upon the medi-astinal space (lungs, pleuræ, and thyroid); (3) metastatic growth from distant organs (breasts, gastro-intestinal tract, especially rectum, uterus, prostate, and kidney); (4) Hodgkin's disease and the leukemias.
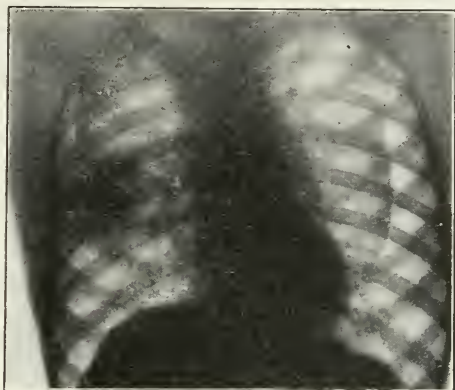
Fig. 11.—M. H., aged thirty-six years (colored). Wassermann positive. Gum-matous formation in the mediastinum (cystic) and gumma in the right middle lobe; no pain. Stridulous type breathing; expiratory type of dyspnea; aphonia; emacia-tion.
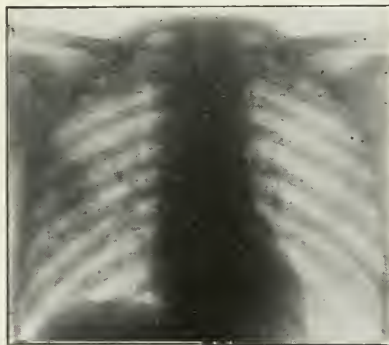
Fig. 12 —M. H. (colored), showing effects after two months of antiluetic treatment

Among the rarer forms he also mentions fibromas, lipomas, myomas, etc., and gummas. He points out that the more common growths of the mediastinum are, however, sarcomas and carcinomas, and emphasizes the fact that aneurysms may simulate mediastinal growths. As to differential diagnosis of the latter, he states that the general symptoms are those common to malignancy: weakness, loss of weight, secondary anemia with a progression to complete marasmus.

Local symptoms are dependent upon the structures compressed. Dyspnea is the most common.   Pain is usually dull, of aching type, and may be located quite remote from the neoplasm.

With growths in the posterior mediastinum, causing compression on the emerging nerve roots from the vertebral column, severe pain may be present in the back or along the lateral chest wall.

In a recent article, Guttman and Neuhof[1] offer the following explanation of the marked difference in the two brachial blood-pressures, and in the two radial pulses, in conjunction with laryngeal paralysis, which so closely resembles the clinical syndrome of aortic aneurysm: "That the dilated pulmonary artery was probably wedged in with sufficient force under the aortal arch, and especially opposite the origin of the left subclavian artery, as to cause interference with the circulation of the latter and consequent difference between the two sides in the brachial blood-pressure and in the radial arteries."

The extrabronchial causes of tracheobronchial stenosis, according to Lord,[2] require differentiation.

These extrabronchial causes comprise, for the most part, diseases which develop in or about the mediastinum or invade this region, as in a case of malignant disease by metastasis.   They may also give indication of their presence by the aneurysmal syndromes before mentioned, i. e., by dulness in the supracardiac region or over the vertebra between the third and ninth dorsal spine and such signs of pressure upon other organs as dysphagia, inequality of the pupils, or the pulses, variation in the blood-pressure in the two arms, "tracheal tug," recurrent laryngeal paralysis, engorgement of the vessels of the head or neck or one arm, and dilated superficial thoracic veins.

The history of syphilis, attacks of pain like angina pectoris, pulsation of the dull area, systolic thrill and murmur, diastolic shock, and aortic regurgitation speak for aneurysm.

Cachexia and enlarged cervical or axillary glands suggest malignant disease.

Mediastinal involvement in a child with tuberculosis is likely to be due to enlarged and tuberculous glands.

Examination with the roentgen rays is important and may lead to the detection of extrabronchial disease, of which there is no indication on physical examination.

Syphilis of the lung, more especially in reference to gummatous formations, may simulate aneurysm.   Such a diagnosis may be based on: (a) Knowledge of syphilitic infection followed by secondary manifestations and the coexistence, with the pulmonary processes, of other tertiary syphilitic lesions; (b) ulceration or stenosis

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[1] Radial Pulse Difference and Left Recurrent Nerve Paralysis Due to Mitral Stenosis, Jour. Am. Med. Assn., January 29, 1916, p. 336.
[2] Diseases of the Bronchi, Lungs, and Pleuræ.

of the trachea or bronchi, wherein is suggestive evidence; (c) positive Wassermann reaction; (d) the roentgen-rays.

As to gummas, according to Lord, these may be found in any part of the lungs, more commonly within than on the surfaces. Favorite sites for this lesion are the middle lobe of the right lung principally and in the hilum, and are usually without symptoms.

Cough and dyspnea are frequently met with; pain is rarely experienced. Emaciation may exist, with extensive pulmonary disease, as seen in diffuse fibroid induration.

It is to be noted in closing that the thymus gland may degenerate and undergo sarcomatous changes and may simulate aneurysm, thus calling for differentiation.

I wish especially to emphasize that there is no one single physical sign of aneurysm which may not be produced by other conditions than aneurysm. Moreover, it is extremely difficult to differentiate between a transmitted pulsation and a true expansile pulsation. The uniform method of checking all physical examinations of the chest in doubtful cases with the fluoroscope or roentgen-ray plates is to be commended as the only means which will lead to more accurate and early diagnosis of mediastinal conditions.

THE SIGNIFICANCE OF URETERAL TUBERCLE BACILLURIA.[1]

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NEW YORK.

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The problem that I propose to lay before you tonight is replete with difficulties, and may be encountered by anyone who deals with patients suffering from urogenital tuberculosis. I fear that in this field very few categorical statements are permissible, and that in each individual case the surgeon will have to carefully weigh the evidence before arriving at the conclusion that he is dealing with a case of renal tuberculosis or not. In my experience with cases of genital tuberculosis this problem has been most complicated, and in a perusal of the scanty literature I find that others have met very much the same difficulties as I have encountered. A failure to properly interpret the clinical findings has repeatedly led clinicians astray and has suggested the belief that occasionally patients suffering from renal tuberculosis are cured by non-surgical procedures.

A brief review of the following published cases will illustrate

[1] Read before the Genito-urinary Section, New York Academy of Medicine, February 21, 1917.

some of the difficulties to which I wish to refer. In Kielleuthner's excellent paper[2] he cites two very instructive cases in which the interpretation of the findings, *i. e.*, the significance of ureteral tubercle bacilluria, is by no means clear.

Case I (Israel).—In this patient the right kidney was recognized as tuberculous by all the usual criteria, including the presence of tubercle bacilli. The bladder was moderately ulcerated. In the urine from the left (second) kidney there was albumin, otherwise negative, but the guinea-pig inoculation was positive. What was the significance of this bacilluria? Did it signify renal tuberculosis of the second kidney? Did it point to an excretory bacilluria from a non-tuberculous but moderately impaired second kidney? or was it an accidental contamination of the ureteral specimens in the catheter's intravesical transit? As the patient was well three years later, one might suspect a spontaneous cure, though it is much more likely that the second kidney was not tuberculous and that the positive guinea-pig test was explicable by contamination or by an excretory bacilluria. The latter view of an excretory bacilluria is accepted by Israel and Kielleuthner.

Case II (Kielleuthner).—In this patient the left kidney speci- men was typical of renal tuberculosis (turbid, red and white cells, tubercle bacilli). The right kidney showed good indigocarmin out- put, clear urine, with small amount of albumin (0.4 per cent.), few hyaline casts, no microscopic elements. The guinea-pig inocula- tion was positive on both left and right ureteral specimens. The bladder was inflamed, bled easily, had diminished capacity, and showed several typical ulcers. Reëxamination with the greatest care, to avoid contaminations, washing "in and out" through the ureter catheters, gave the same result, guinea-pigs were positive on both sides. Two months after a left nephrectomy for tuberculosis a guinea-pig test on the bladder urine was still positive, and three months later a specimen from the right ureter was negative in an inoculation test. Subsequently reëxamination confirmed this; bladder urine still positive, but right kidney urine negative. The author believes this again illustrates an excretory bacilluria from the right kidney while the left tuberculous kidney was *in situ,* which bacilluria disappeared after nephrectomy. Unfortunately he ignores the fact that, despite the nephrectomy, a tuberculous focus, as proved by positive inoculation from bladder urine, was still in the urinary tract, from which we might expect a continued excretory bacilluria if his interpretation were correct. He also fails to state whether the albumin had disappeared from the urine of the remaining kidney, which, as we shall see, he believes is always present in the cases showing excretory bacilluria. Kielleuthner's interpretation of his facts may be correct, but his reasoning is not

convincing. A contamination, despite great care, of the ureteral catheters in transit through a diseased bladder, as well as a reflux up the healthy ureter, which might produce a contamination, must also be considered as likely sources of the tubercle bacilli that led to the repeatedly positive guinea-pig tests on the healthy side.

CASE III (Bottomley-Cunningham[3]).—In this male patient the diagnosis of right kidney tuberculosis based upon ureteral specimen inoculation tests was made in 1907. A characteristic unilateral genital tuberculosis, going on to abscess formation, was also present. After eighteen months' tuberculin treatment the symptoms (?) were entirely absent, and two years ago (1914) inoculation tests of the urine were negative.

This case might furnish comfort to those who believe that renal tuberculosis might be cured by tuberculin, though the author avoids making any such claim. The question that interests us is, What was the significance of the ureteral tubercle bacilluria on which the diagnosis of right renal tuberculosis was based. It is remotely possible that there was a renal tuberculosis and that hygiene, tuberculin, etc., effected a cure. Until we are sure that the specimens were not contaminated by tubercle bacilli derived from the genital tuberculosis, either by being picked up in the instrument or the catheters, or by reflux up the ureters, or by excretion through a non-tuberculous kidney, the original diagnosis must be looked upon with skepticism.

CASE IV (Brown[4]).—Male, aged twenty-eight years, consulted a physician for eugenic purposes before marriage. His urine contained albumin, and a specialist found tubercle bacilli in the urine from the right kidney. A second specialist could not corroborate these findings, but suspected that the diagnosis of right renal tuberculosis was correct. While under hygienic therapy the sediment of his bladder urine was inoculated into guinea-pigs, with negative results. He gained in every way, and six months later developed a tuberculous epididymitis, which was removed. Then the suspicion that the right kidney was tuberculous was again entertained.

From the few data in the case report, renal involvement cannot be excluded. On the other hand it is not at all unlikely that the genital tract may have been diseased at the first cystoscopy, and contaminations might have taken place.

From these brief preliminary remarks it must be evident that the significance of ureteral tubercle bacilluria is not as easily described as we would desire.

Tubercle bacilli may be present in ureteral specimens under three conditions, even though their presence usually indicates a renal tuberculosis.

[3] Surg., Gynec. and Obstet., October, 1916.
[4] Jour. Am. Med. Assn., March 13, 1915, p. 887.

I. When there is a tuberculous focus in some other part of the body and the bacilli are excreted from a non-tuberculous kidney.

II. When there is a tuberculous focus in the genital or urinary tract by contamination or by ureteral reflux.

III. When the tuberculosis is in the upper urinary tract or kidney.

I. A great deal of work has been done on excretory tubercle bacilluria, but much of it is almost worthless, as it lacks the completeness of careful scientific work. Moreover, much of the best work is partly contradictory.

Foulerton and Hillier[5] examined 18 cases of advanced chronic pulmonary phthisis and found by inoculation tests 9 positive tubercle bacillurias, using bladder urine. At autopsy 6 showed no urinary tuberculosis. In this paper the necropsy reports are so brief, and regularly omit all mention of the condition of the genital tract, that one must be loath to accept the data as published. All the more so as Cunningham,[6] in a more careful study, reports that in 66 cases with advanced pulmonary tuberculosis he obtained 6 positive inoculations. He then collected the urines in those 6 cases with ureteral catheters and failed to corroborate the earlier findings in 4 cases.[7] In one of the remaining 2 cases there was a genital tuberculosis which he admits as a possible source of the bacilli, while in the remaining case, owing to the patient's death, further study was impossible. (Autopsy refused.)

Opposed to this careful work of Cunningham, more recently Bernstein[8] and Brown[9] report 10 per cent. positive inoculations under practically the same conditions, but their observations are so incomplete that one cannot but hesitate to accept them as indicative of excretory bacilluria.

Kielleuthner[10] also contributed a careful paper on this subject. He studied only males with phthisis. In 13 such cases, with albumin-free urine, with complete genito-urinary macroscopic and microscopic autopsies, all inoculation tests were negative. In 11 similar cases with albumin in the urine and non-tuberculous urogenital tract 3 inoculation tests were positive. From these series he concludes that the tubercle bacilli do not pass normal kidneys, but that when the kidneys are impaired, as evidenced by slight albuminuria, the bacilli may pass and an excretory tubercle bacilluria may develop. In the cases (Nos. I and II) previously quoted he applied these facts to interpret the presence of the bacilli in the urine of the second kidney.

It would therefore appear that in advanced tuberculous lesions

[5] British Med. Jour., 1901, p. 774.
[6] Boston Med. and Surg. Jour., 1911, p. 872.
[7] Possibly clinically hidden cases of prostatic tuberculosis.
[8] New York State Med. Jour., 1914.
[9] Loc. cit.   [10] Loc. cit.

excretory tubercle bacilluria may occur, even though the incidence varies so greatly in the work of different careful students.   In less advanced lesions, judging from the isolated cases published, this seems to be a much more unusual occurrence.   Rist and Kindberg[11] report two positive inoculations with urine from a patient who at autopsy showed only a sclerosed apical lesion, from which in turn tubercle bacilli were obtained (inoculation test).   Wildbolz[12] reports a patient who passed tubercle bacilli through a diseased stone-bearing kidney and showed no distinct evidence of tuberculosis in her other organs.   After pyelotomy the urine became clear and a subsequent guinea-pig test (one and one-half years later) was negative.   Records of other similar cases of excretory tubercle bacilluria associated with stone or with tumor have been published, but do not bear close scrutiny, as too many sources of errors are apparent.

II. How often a tubercle bacilluria (non-excretory) occurs in tuberculous lesions of the genital tract has not been studied sufficiently as yet.   Cunningham[13] found bacilli in 15 per cent. (in smears) from expressed prostates in cases of tuberculosis of the epididymis.[14]   In inoculation tests their presence would probably be more frequent.   Without autopsy work it will be well-nigh impossible to answer this question accurately, as when bacilli are present in the bladder urine in such cases it will often be most difficult to prove without autopsy that the kidney or kidneys are not contributing to the bacilluria that is present.   It is in just these cases that one finds the greatest difficulty in interpreting the significance of ureteral tubercle bacilluria.   It would be interesting to know how often normal kidneys are removed in just this type of case when the diagnosis is based upon the finding of tubercle bacilli in the ureteral specimen.   As I see it such specimens may obtain their quota of bacilli in three ways when the kidneys are not tuberculous:

(a) As an excretory phenomenon.

(b) As the result of reflux up the ureter of bladder fluid containing bacilli.

(c) As gross contamination of the cystoscope or catheters despite the greatest care.

(a) It is perfectly conceivable that with tuberculosis of the genital tract an excretory bacilluria may take place.   There is no valid reason for denying this possibility if we admit the validity of the proof just referred to, in which more distant foci of tuberculosis lead at times to a tubercle bacilluria.   Naturally one would

[11] Presse méd., 1914, p. 177.   [12] Nierentuberkulose, 1913.
[13] Loc. cit.
[14] In 51 cases he examined the bladder and kidneys and found the bladder involved in 16, one kidney involved in 9, both kidneys involved in 5. His data for such diagnoses are not given.

wish to apply a simpler explanation to this phenomenon; such an explanation as is offered by a reflux from the bladder up the ureter or by a gross contamination. Still, in spite of one's inclinations I believe such a possibility as excretory tubercle bacilluria from a focus in the genital tract cannot be absolutely denied.

(b) When we come to the other possible explanations I believe we are on safer ground. Recently, Kretschmer has again called attention to the possibility of a reflux from the bladder up the ureters and has published excellent roentgenographs showing this phenomenon. I have repeatedly proved this both by using colored solutions in the bladder and recovering same from the ureteral catheter *in situ* as well as by roentgenograms with argyrol. This phenomenon occurs with what appears to be normal ureteral orifices sufficiently frequently to throw doubt on the absolute purity of ureteral specimens. It might be avoided by emptying the bladder of all its fluid as soon as the ureters are catheterized, but even then it may be too late, as bladder fluid containing bacilli may already have entered the ureteral lumen. The presence of the catheter in the ureter appears to affect the complete closure of its lower end, in this way permitting a reflux. But even when no catheter is in the ureter this occasionally occurs, as I have recently shown in a patient presented before the New York Surgical Society[15] in an argyrol cysto-ureterograph.

(c) Moreover, in introducing the cystoscope if tubercle bacilli are present in the urethra as well as in the bladder, most painstaking washings may fail to get rid of all the bacilli and thus allow of contamination of the ureteral catheters in transit to the ureteral meati.

The Brown-Buerger cystoscope with its separated catheterizing system would seem best calculated to prevent such occasional contaminations, though some surgeons, for example Casper,[16] think that it is easy to prevent the introduction of tubercle bacilli that may be in the bladder into the ureters. This leads him to the conclusion that tubercle bacilli in ureteral specimens mean renal tuberculosis. Einar Key,[17] having experiences similar to mine, admits that in unilateral renal tuberculosis, vesical tuberculosis and prostatic tuberculosis, such contaminations may take place and can be in a measure controlled by using a special type of closed cystoscope (Dingel). With this instrument I have had no experience. My technic is the following:

To guard against these contaminations the bladder is thoroughly washed through the sheath of the cystoscope and then the catheterizing system, with pins in the catheters, is introduced. Only after the ureters are catheterized are the pins removed and only

[15] Ann. Surg., 1916, v: case of prostatic and ascending renal tuberculosis.
[16] Verhandl. d. Deutsch. Gesellsch. f. Urolog., 1911, p. 57.
[17] Hygiea, 1908.

the later specimens (third and fourth) are used for tubercle bacillus examinations and inoculations.

II. In addition to the two sources just mentioned the excretory bacilluria and that due to some kind of contamination, there is the common source of tubercle bacilluria, renal tuberculosis. With careful work the bacilli can be demonstrated in the smear in over 80 per cent. of the cases of kidney tuberculosis and in probably a higher percentage in inoculation tests. The greater sensitiveness of the guinea-pig test is admitted rather generally, and there is no doubt that it is a *sine qua non* of accurate work in the recognition of tuberculosis in the genito-urinary tract. For some time I was under the impression that a positive inoculation test or a smear from a centrifugalized ureteral specimen which showed tubercle bacilli pointed definitely to the diagnosis of renal tuberculosis. If, moreover, the slide showed some pus cells plus tubercle bacilli, despite good function, I believe I was justified in making the same diagnosis and recommending nephrectomy. In view of the experiences gathered in a series of 8 cases I have been considerably shaken in my earlier convictions. Three of these cases I have selected, as they illustrate the great difficulty presented in interpreting the significance of ureteral tubercle bacilluria.

The cases that I wish to report are arranged in definite sequence, based upon the lesser or greater probability of renal involvement. The first case, despite the fact that it has many of the ear-marks of renal tuberculosis, I am pretty well convinced has no such involvement; the second case is to my mind less definitely free from renal tuberculosis; while the third is so similar in many respects to cases of renal tuberculosis that I have not the hardihood to declare against that diagnosis. Though I am inclined to regard all three cases as tubercle bacillurias without renal involvement, I feel so insecure in my position that I am laying the facts before you for discussion. With the facts, such as they are, I am, however, convinced that nephrectomy is not indicated.

CASE I[18] (972).—M., aged thirty years. In March, 1916, patient began to have some discomfort in left side of lower abdomen. In April the left epididymis became involved.

May, 1916. Examination showed a fairly well-nourished man, with definite tuberculosis of left epididymis. The vas was normal. Nothing abnormal palpable by rectum except slight induration about the right vesicle. The urine was clear and brilliant, but became turbid after gentle pressure on the prostate. Examination of urine voided before palpation of prostate showed many pus cells, a few red blood cells and epithelial cells, numerous tubercle bacilli in small groups and isolated. After palpation of prostate and vesicles, in the turbid voided urine, the pus and red cells were

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[18] Histories are abbreviated. The careful bacteriological work was done by Dr. H. L. Celler.

more numerous, and the tubercle bacilli were much more readily found.

There was no pain on urination and no frequency. No other evidence of tuberculosis was detected. There was no cough and no night sweats.

The patient was placed on hygienic treatment, sexual intercourse was interdicted, roentgenotherapy was applied to the epididymis and to the prostate.

June, 1916. Weight has increased nine and one-half pounds. Urine is clear and brilliant. Microscopic examination of centrifugalized specimen shows less pus and less tubercle bacilli. Despite roentgenotherapy the disease in the epididymis is extending.

October, 1916. Has had nine intensive roentgen-ray applications. Disease has involved the whole left epididymis. Urine is brilliant and there are no vesical symptoms. Tubercle bacilli are present in voided urine, also faint trace of albumin, many red cells, and few pus cells.

November, 1916. Cystoscopy showed normal bladder and normal ureteral meati. There was slight bulging over the position of the prostate. Three specimens collected from each kidney. The indigocarmin output was strong and equal in both sides. In the posterior urethra there was slight play of prostatic lobes. In left sulcus there was purulent discharge. No ulcers seen. After centrifugalizing kidney specimens no visible sediment was obtained on either side. Smears from the left kidney showed tubercle bacilli in fairly large numbers, a very few leukocytes and red cells. Smears from the right kidney showed no tubercle bacilli, but rather more white and red cells than on other side. Two guinea-pigs were inoculated[19] from the last specimen from each side. Those inoculated with the urinary sediment from the left kidney died in one week and showed no tuberculosis; those from the right kidney lived six weeks and were negative.

Rectal examination showed left half of prostate elastic and larger than right.

November 15. Removal of left testis for extensive tuberculosis of epididymis and adjacent testis. From this patient made an uneventful recovery, and after spending two weeks in the country, where he gained about ten pounds, a cystogram was taken to determine whether the left ureteral orifice was patulous or not. No ureteral ascent took place even when the patient strained against the tied-off urethra. The voided urine is still brilliant, though in the first glass there are a few flocculi. The catheterized bladder urine continues brilliant and clear. Its sediment contains tubercle bacilli and pus cells. There is no kidney sensitiveness and there are no vesical symptoms. Patient feels perfectly well (February, 1917).

[19] Intra-abdominally and in groin.

Remarks. What is the significance of the tubercle bacilluria in the specimen from the left ureter? Do they indicate left renal tuberculosis? are they the result of an excretory activity of a non-tuberculous kidney? or are they present as the result of a contamination or a reflux?

I admit that a renal tuberculosis cannot be excluded. The continued absence of all vesical symptoms of the equal function of the two kidneys as well as the brilliantly clear vesical urine suggest that the kidney is not tuberculous. Are we then dealing with an excretory phenomenon or a contamination? To differentiate between these two possibilities appears well-nigh impossible.

CASE II[20] (391–917).—M. J., aged thirty-five years. As a child he had a tuberculous infection of the knee; since then has had no further sign of any tuberculous disease. In 1912 the patient developed some vague pleural irritative signs at his left base, which cleared up slowly. Thereafter he developed a series of urinary symptoms that gave him considerable distress. He had marked pain at the end of urination, with increased frequency, and the appearance of blood. There had been no lumbar pains and no colic. He had never passed sand or gravel. Examination of his bladder urine obtained by catheter showed enormous numbers of tubercle bacilli. The slide which I examined was literally covered with Koch bacillus. Physical examination showed a young man without any pulmonary involvement. There was no kidney tenderness, and the kidneys were not palpable. His prostate was smaller than normal, the right half impressing me as slightly atrophic. The testes were normal. Cystoscopic examination was made under the impression that the patient was suffering from a secondary vesical tuberculosis, with a primary focus in the left kidney, to which I had ascribed the earlier symptoms at the left base.

March 1, 1912. Cystoscopy and ureter catheterization. Bladder mucosa was deeply injected in trigone down to the neck. Edema well marked here, and this area bleeds readily. No ulcers and no tubercles were seen. Both ureteral meati were small but normal in appearance, without any periureteral injection or edema. Both ureters were catheterized and almost clear urine was obtained. Left kidney: albumin, 0; urea, 1.3 per cent.; few red and pus cells. Right kidney: albumin, 0; urea, 1.5 per cent.; occasional red cells; very few pus cells. Within seventeen minutes there was a strong discharge of indigocarmin on both sides. Cultures from the bladder and from each of the kidneys were sterile. Careful search in slides from the kidney urines, carried out by three examiners, one of whom spent eight hours in the search, failed to show any tubercle bacilli. This might occur despite the presence of a renal tuberculosis, though

it was surprising in view of the myriads that had just been found in the bladder specimen, recovered at this examination.

Urine from both sides inoculated into guinea-pigs gave positive results.

After the cystoscopy the patient was kept in bed and the vesical symptoms gradually disappeared. Still, the bladder specimens contained tubercle bacilli, and my attention was naturally directed to the lower tract. I catheterized the bladder before and after gentle massage of the prostate and found what we took to be an increase of bacilli in the second specimen. This I regarded as presumptive evidence of local disease, and to test this conclusion, which was so opposed to my original interpretation, I decided to use the tuberculin test.

Under 1 mg. of tuberculin all the vesical symptoms returned—hematuria, pain, and increased frequency. At the same time there was a mild febrile reaction and locally the half of the prostate that I had regarded as atrophic became markedly tender for the first time. This reaction rapidly subsided and the patient was placed on therapeutic doses of tuberculin, with the result that all the symptoms of vesical irritation disappeared, and no tubercle bacilli or red cells were to be found in his urine during the next six months.

Until November, 1915, patient continued well and had no vesical symptoms. Throughout this time he states his urine has been clear, and I have seen it on and off and found it brilliant and absolutely clear. In November, 1915, a few months after his marriage, bladder irritability began anew and lasted one week. In January, 1916, another attack of bladder irritability, with burning pain at end of urination. Day frequency was normal and at night voided once. There was pressure in the perineum. The voided urine contained a few red cells, numerous pus cells, tubercle bacilli, and a faint trace of albumin. Patient went to the West Indies, discontinued sexual intercourse, and felt well until March, when he had another attack. In April, 1916, he was examined in another clinic, with the following results:

Cystoscopy showed "a trigone hyperemic and hypertrophied, with bits of adherent mucus but no definite ulceration. Both ureteral orifices were apparently normal. The specimen from the right ureteral orifice showed an occasional white cell, no tubercle bacilli. The specimen from the left ureter showed many pus cells and a few definite tubercle bacilli. The functional test showed 18 c.c. excreted from the right side, with 15 per cent. phthalein and 28 c.c. excreted from the left side in half an hour with 17 per cent. phthalein." Guinea-pigs inoculated from both sides were positive. On these findings the diagnosis of left renal tuberculosis was made and nephrectomy advised.

I saw the patient on April 25, 1916, when there was no kidney tenderness but slight tenderness over the prostate per rectum.

The first urine was clear but contained a few flocculi. The catheterized specimen was macroscopically clear, but contained pus cells and tubercle bacilli. After gentle massage of prostate with the catheter in the posterior urethra, blood and frank pus were obtained.

Cystoscopy showed normal bladder except just behind the left ureter orifice and over a moderately bulging prostate, where two very small, probably traumatic, submucous hemorrhagic areas were visible. There was slight hyperemia about the right ureter orifice but none about left. The indigocarmin output was intense in sixteen minutes and equal on both sides. Rectal examination showed the right half of the prostate smaller than the left, and this smaller half was slightly tender. The bladder capacity varied from 12 to 19 ounces, and there was no frequency; no night urination.

The examination of the *bladder specimens* obtained at cystoscopy showed: albumin, a trace; urea, 0.9 per cent.; epithelial cells; many pus cells; moderate number of red cells, with tubercle bacilli in clumps.

The right kidney specimen showed: no albumin; urea, 0.9 per cent.; epithelial cells; occasional leukocytes; no red cells. No tubercle bacilli found.

The left kidney specimen showed faint trace of albumin, urea 1 per cent., epithelial cells, moderate number of white cells and small number of red cells, together with isolated tubercle bacilli.

Two guinea-pigs inoculated with sediment (centrifugalized) and with supernatant fluid from the right kidney developed tuberculosis. Of two guinea-pigs inoculated with sediment and with supernatant urine from left kidney, the former was positive and the latter negative.

Since this cystoscopic examination the patient has been under regular observation. He has no increased frequency nor nocturnal urination. His voided urine is brilliant but contains flocculi, while the catheterized bladder urine is regularly brilliant and clear, though the microscopic examination regularly shows pus cells and tubercle bacilli. Even after long centrifugalization there is only the slightest sediment. The patient has gained weight and feels perfectly well.

January 6, 1917, his voided urine was reported as follows: Gross appearance; amber; clear; flocculent sediment of mucus; albumin (cold nitric acid test) negative. Microscopic (centrifuged) fresh: moderate number of pus cells and mucus; stained; pus cells, very many tubercle bacilli in smaller and larger clumps.

Remarks. This patient has been under observation for five years —that is, since he first showed a tubercle bacilluria. Originally the inoculation tests from both kidneys were positive, though the slide examination was negative. As the patient had a distinct focus in his prostate and had no symptoms of persisting vesical

irritation, had brilliant clear urine, and normal kidney function, I was inclined to look upon the bilateral ureteral tubercle bacilluria as a contamination or as an excretory phenomenon. Others to whom I submitted the data in this case took Casper's attitude previously mentioned, and suspected a bilateral renal tuberculosis. After a period of quiescence lasting four years the original symptoms recurred, and by two cystoscopists practically the same data are found as at the earlier examination. Both kidneys functionate well; both ureteral specimens induce tuberculosis in the guinea-pig; but now the left kidney specimen contains more white cells than four years earlier and some tubercle bacilli are demonstrable in the smear from this side. Even now the bladder urine is brilliantly clear, though the sediment shows a moderate number of pus cells and tubercle bacilli. There is no frequency, no pain, and apparently the patient is in perfect health.

From all these data it is impossible to exclude a left renal tuberculosis. Such was my original suspicion five years ago. After careful study I felt convinced at that time that the kidneys were normal despite the positive inoculation tests on both sides, even though there were more leukocytes in the left specimen than is normal. What is the significance of the four positive inoculation tests with the right ureteral specimens? Has that always been due, both in the hands of others and of myself, to contaminations? Or is it an excretory bacilluria, derived from the prostatic focus? With such brilliant urine, without any vesical symptoms, with apparently perfect health and gaining weight, I believe I am not justified in recommending removal of the left kidney despite the fact that from this side we recovered nine months ago tubercle bacilli in the smear.

CASE III (1003).—S., male, aged thirty-four years. Previous gonorrheal and syphilitic infection. Since the middle of 1915 swelling of left epididymis, associated with bladder irritability, terminal bleeding, and pain. These persisted for three months. An abscess formed in the left half of the scrotum and discharged pus. Gradually the swollen area diminished, but the sinus persisted.

June, 1916. This condition was still present. There was no vesical irritability. The patient was well nourished, and except for the discharging sinus leading to a tuberculous epididymis and an enlarged left prostatic lobe the patient was in excellent health. His urine was turbid and contained pus cells and tubercle bacilli.

June 23. Cystoscopy showed absolutely normal bladder. The lips of the left ureteral orifice appear slightly separated. After passing ureteral catheters some indigocarmine was introduced into the bladder, and it was recovered through the left ureteral catheter proving a definite reflux up this ureter. Subsequent argyrol and roentgen-rays, with bladder filled and patient in the Trendelenburg position, showed no ascent (really descent) up the ureters. The

left kidney shadow was normal in size. The bladder urine (by catheterization) showed a faint trace of albumin, many white and red blood cells, and many clumped tubercle bacilli. The left kidney specimen showed urea 0.2 per cent., a few white and red blood cells, and tubercle bacilli. The right kidney specimen showed: urea, 0.8 per cent., and epithelial cells and cylindroids. Guinea-pig inoculation from right side was negative.

June 24. Partial orchidectomy and epididymectomy (left side). After recovery from this operation the patient went to the country and gained almost twenty pounds. On his return in November he felt perfectly well, had no vesical symptoms and no tenderness in the lumbar region. In the left scrotum there was a narrow sinus and several, probably tuberculous, nodules. The voided urine was turbid while the catheterized bladder urine was much clearer. Both contained pus cells and tubercle bacilli. The bladder was thoroughly irrigated with 2500 c.c., and the terminal wash fluid was examined for tubercle bacilli, which could not be found in the smear but where demonstrable by the inoculation test, thus showing how difficult it is to wash the bladder clear of tubercle bacilli.

December 1. Cystoscopy shows a congested trigone. There is no evidence of disease in the bladder except a longitudinal area overlying the left vesicle to the outer side of the left ureteral orifice, where the mucous membrane is injected, edematous, and pushed forward by the underlying tuberculous left seminal vesicle. The right ureter admitted a catheter readily, and while the catheter was *in situ* 10 cm. up the ureter, an indigocarmine reflux up this ureter was demonstrable. The left ureter admitted a catheter 3.5 cm., and at this level it was obstructed. The catheterized bladder specimen showed a heavy sediment containing pus and epithelial cells. No red blood cells. Many tubercle bacilli. The specimen from the right kidney showed urea, 1.8 per cent.; no tubercle bacilli; a few red cells and epithelial cells. The specimen from the left kidney showed urea, 1.1 per cent.; very few tubercle bacilli; pus cells much less numerous than in bladder specimen; many epithelial cells, few red cells. The inoculation tests were positive on left side and both pigs used for the right side were negative.

February 5, 1917. Patient is in excellent condition. Has no frequency of urination and no pain.

Remarks. In this patient there is a definite left-sided genital tuberculosis, with pus and tubercle bacilli in his catheterized bladder urine. At the first cystoscopy a definite reflux up the left ureter was demonstrable, and the suspicion was entertained that this might account for the presence of the few tubercle bacilli and few pus cells as well as the apparently lower urea output on this side. Almost six months later, without the development of signs pointing to a definite renal involvement, a reëxamination was made, and now there was cystoscopic evidence of marked disease

of the left seminal vesicle, with obstruction to the passage of the ureteral catheter beyond 3.5 cm. Now there were more pus cells in the left kidney specimen than before. Does that mean left renal tuberculosis or does it point to a ureteritis of the lower end of this ureter, due to the marked inflammation of the adjacent seminal vesicle? Naturally a renal tuberculosis cannot be excluded. I am at a loss to interpret the significance of the ureteral tubercle bacilluria. It may owe its origin to any one or all three of the factors to which I have repeatedly called attention in this discussion.

In closing, I am in the unfortunate position that, despite careful study, I can make no categorical statements as to the significance of the ureteral tubercle bacilluria, and I come back to my opening remarks that each case must be decided upon its merits, and only after such careful study as each patient will permit may we be in a position to decide as to whether the tuberculous disease has involved the kidney or not. Before one has reached a definite decision that the ureteral tubercle bacilluria is due to renal tuberculosis, the next step, removal of the kidney, must be relegated to the future.

ALBUMINURIA AND HEMATURIA FOLLOWING THE ADMINISTRATION OF HEXAMETHYLENAMIN.

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Nicolaier, in 1894, was the first to note the fact that painful micturition and hematuria may at times result from the administration of hexamethylenamin even when given in small amounts. The occurrence of albuminuria and hematuria has been discussed from time to time, nevertheless the number of reported cases is not large and the subject has not received the attention it deserves. The following 5 cases are of interest:

Case I.—N. R., aged two years, during an attack of acute otitis media was given hexamethylenamin, gr. iiss, every four hours. No symptoms of urinary irritability were noted, but three days later the urine examination was as follows: Normal color; moderately turbid; contains a number of large shreds; acidity 110 degrees; 1023; albumin 0.25 per cent.; sugar and indican absent; aldehyde test negative. The microscope showed large numbers of blood and pus cells. The hexamethylenamin was discontinued, and six days later the urine had again become normal.

Case II.—Miss M., aged twenty-one years, was under treatment for neurasthenia and intestinal putrefaction. On August 6, 1913, the urine was bright green in color; moderately turbid; acidity 140 degrees; 1020; albumin and sugar absent; indican enormously

increased. The green color may possibly have been due to chemical changes in the large amount of indican which was present. The patient was ordered to take gr. x of hexamethylenamin three times daily. On August 11 she stated that for several days she had been troubled with severe pain and burning upon micturition, and on one occasion had noticed several small, flesh-like pieces in the urine. On that day the urine was very turbid; contained many large shreds; albumin ring very dense; indican moderately increased; the microscope showed many pus cells; squamous epithelium; uric acid and bacteria. After withdrawal of the hexamethylenamin the urinary irritability and the albumin disappeared.

CASE III.—W. W., aged twenty-seven years, seen April 18, 1913. The patient had suffered repeated attacks of rheumatic fever and presented a chronic tonsillitis and a severe aortic and mitral endocarditis. The urine was of normal color; acidity 42 degrees; no albumin or sugar; indican moderately increased. He was ordered to take gr. xx of hexamethylenamin three times daily. When seen two days later he stated that about half an hour after the first dose of medicine he began to have burning urination. This increased in severity until the distress became very acute and the urine markedly bloody. Examination showed the urine to contain a large amount of blood; acidity 50 degrees; albumin a large trace. The hexamethylenamin was at once withdrawn, but the patient possibly may have decided to run no further risks, for he did not return for observation.

CASE IV.—Miss W., aged eighteen years, seen March 10, 1912, presented signs of an infection of obscure origin, involving the urinary tract. March 12 urine examination was as follows: Very turbid; dirty yellow; acidity 110 degrees; 1025; slight trace of albumin; marked excess of indican; blood and pus cells frequent; squamous epithelium; urates and numerous bacteria. March 16 the albumin had disappeared. A prescription containing gr. v of sodium benzoate and gr. x of hexamethylenamin was given, to be taken three times daily. March 19 the urine showed a large amount of albumin, estimated at $\frac{1}{8}$ per cent., and an increased amount of blood. Five days later, March 24 the albumin had increased to 0.5 per cent., Esbach. The patient complained of some pain and burning on passing urine. The hexamethylenamin was withdrawn, and eleven days later, May 4 the albumin had entirely disappeared. A few days afterward the hexamethylenamin prescription was again started, but on May 17 the urine presented a large amount of albumin, estimated at 0.25 to 0.5 per cent. When the hexamethylenamin was a second time withdrawn the albumin promptly subsided to the usual slight trace. The signs of urinary infection continued for over a year, and June 13, 1913, helmitol, a citric acid salt of hexamethylenamin was prescribed in doses of gr. v, t. i. d. The urine on that day showed only the slightest possible trace of albumin.

No symptoms of urinary irritation were noted, and three days later the dose was increased to gr. x three times daily.   June 15 five days after the administration of helmitol had been begun, the urine showed 0.25 per cent. of albumin, with considerable blood and pus. The helmitol was promptly discontinued and the urine again returned to its usual condition, showing only the slightest possible trace of albumin June 23.

Systematic investigation of the urinary tract proved the infection to be limited to the bladder.   Bacteriological examination of the urine showed the Bacillus coli communis, together with other unidentified forms.   Several examinations of the catheterized urine failed to reveal tubercle bacilli, and guinea-pig inoculation was negative for tuberculosis.

Case V.—Miss F., aged thirty-five years, consulted me June 26, 1915, for a subacute cystitis.   She was treated by bladder irrigations with silver nitrate solution.   Because of the alkaline reaction of the urine, acid sodium phosphate was given in addition to hexamethylenamin.   On two occasions symptoms of urinary irritability appeared, together with slight albuminuria.   In each instance the urinary acidity was very high, 70 and 110 degrees respectively.   After a brief withdrawal of both drugs the disagreeable symptoms promptly disappeared.

Less than a decade ago, Crowe and others showed that after the ingestion of hexamethylenamin the drug could be demonstrated in practically every fluid of the body.   These investigations led to the hope that we were in possession of a therapeutic weapon which would prove to be of great efficiency in many infectious diseases. Practising physicians began to use hexamethylenamin in a wide variety of infections (many still continue to employ it), expecting it to present the same striking benefits already observed in certain urinary disorders.   The results have usually proved disappointing, and further laboratory studies have already shown the reasons for failure.

The therapeutic effects of hexamethylenamin depend entirely upon its conversion into ammonia and formaldehyde.   Hexamethylenamin itself has no antiseptic action, even in as strong a concentration as 10 per cent., and the only object in giving the drug is to administer weak formaldehyde.   The liberation of formaldehyde may possibly occur to a slight extent in neutral or weakly alkaline solutions, particularly if exposure to the action of the drug continues for considerable time, but for practical purposes no formaldehyde is formed save in an acid medium.   Urine, gastric juice, and sweat are the only acid secretions of the body, and the therapeutic action of hexamethylenamin must therefore be limited to these secretions.   Not only has hexamethylenamin been found in practically all normal body fluids, but likewise in various pathological exudates, such as serous effusions, pus accumulations, discharge

from otitis media, etc.; yet competent investigators have been unable to demonstrate the presence of formaldehyde in any of these fluids.

The liberation of formaldehyde from hexamethylenamin depends upon three factors: the concentration of the drug, the duration of its action, and the acidity of the medium. These facts have practically limited its therapeutic application to diseases of the urinary tract, principally those of the bladder, although further study may show it to be of service in stomach diseases or in certain skin disorders accompanied by acid sweat.

The longer the urine is retained in the bladder and the higher its acidity the greater will be the formaldehyde production. Degrees of acidity less than 20, expressed in terms of decinormal sodium hydrate, are not favorable. In strongly alkaline urine the drug is useless, but in such a condition acid sodium phosphate (not the sodium phosphate commonly used) may be administered to render the urine acid. To give hexamethylenamin in combination with an alkali is entirely irrational.

Clinically the best results of hexamethylenamin medication are seen in the urinary bladder. Here we have an acid medium, a favorable temperature, and an exposure of the urine to the action of the drug for a variable period, often several hours. It is believed that hexamethylenamin is not broken up into formaldehyde and ammonia until it reaches the bladder. This would explain its disappointing action in many cases of pyelitis and other kidney diseases. In certain individuals, particularly if the urine presents a high degree of acidity, it is possible that formaldehyde conversion may occur in the kidney itself. Even in these cases, however, the urine is passed along into the bladder so rapidly that any therapeutic action is questionable. The possibility of renal irritation from the formaldehyde, which perhaps is occasionally split off in the kidney, must be kept in mind. Under ordinary conditions, however, hexamethylenamin causes no irritation of the kidneys.

When untoward effects appear during the course of hexamethylenamin administration they usually may be traced to the following causes: Insufficient dilution of the drug, high urinary acidity, or personal idiosyncrasy. The most common symptoms are those of vesical irritability, and may vary from slightly increased frequency of micturition to severe vesical tenesmus or even strangury. Albumin or blood is often present in the urine. Unless obscured by blood the macroscopic appearance of the urine is very characteristic. It is pale in color, turbid from pus cells, and shows a large number of flakes and shreds which are different than those seen in any other condition. The source of the blood found in patients showing urinary irritation is probably the bladder. Crowe reports that in dogs in whom an experimental hematuria had been produced by enormous doses, after the subsidence of acute symptoms, microscopic

examination of the kidneys failed to disclose any evidence of permanent damage. Of 95 patients who had received an average daily dose of 75 grains for ten days, painful micturition and hematuria occurred seven times. In 3 of the cases which came to autopsy it was apparent that the hematuria had its origin from the mucous membrane of the bladder and was not due to acute renal irritation. In the remaining 4 cases the urine rapidly became normal upon the withdrawal of the drug.

The source of the albumin found in similar cases has not been conclusively demonstrated. Levy and Strauss believe that individuals with a high urinary acidity may liberate formaldehyde in the kidneys, and under these conditions may develop hematuria or albuminuria. In the writer's cases no renal elements were found in any of the specimens of urine examined, yet the large amount of albumin present in some instances pointed to a kidney rather than a bladder origin.

The treatment of irritation of the urinary tract following the administration of hexamethylenamin is simple. Withdraw the drug, give large amounts of fluid, together with alkalies, and in a short time conditions will almost invariably return to normal. If hexamethylenamin were always prescribed with large quantities of fluid, many, although not all, cases of irritation would be avoided.

In the treatment of pyelitis and other kidney conditions, results cannot ordinarily be obtained unless large doses are given and the urine is highy acid or is rendered so, preferably by acid sodium phosphate. Such patients must be carefully watched for signs of urinary irritation.

A study of the writer's cases leads to the conclusion that the most important cause of albuminuria or hematuria following the administration of hexamethylenamin is abnormally high urinary acidity. In 4 out of the 5 reported cases the acidity was above 100 in terms of decinormal sodium hydrate, and in Case II, it reached the exceedingly high figure of 140. It is therefore necessary to carefully determine the urinary acidity of all patients who are taking hexamethylenamin. If the acidity becomes too low or disappears entirely the drug is inefficient, whereas with a high degree of acidity, irritative symptoms are likely to appear. High dilution of the urine impairs the formaldehyde action; concentratration of the urine increases formaldehyde activity, but favors unpleasant results. The physician must therefore steer a middle course.

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TUBERCULOUS PERITONITIS.

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Tuberculous peritonitis is a condition that occurs much more frequently than is recognized, because, (1) it occurs in a latent form without symptoms and is discovered only at autopsy or during laparotomy for other conditions, and (2) its manifestations are so varied that the diagnosis is often obscure. This is true particularly of the localized forms. The history of many cases of tuberculosis of the peritoneum is that of recurrent attacks of abdominal symptoms with intervals of freedom from the symptoms. It is only when the process becomes extensive enough or gives sufficient evidence on examination to warrant a diagnosis that the condition is recognized. Many of these, in view of the tendency to spontaneous recovery, never reach this stage, and the disease becomes limited before recognized or even suspected. The cases that are diagnosed, therefore, are usually advanced cases. Tuberculous peritonitis may occur at all ages, but its occurrence is noted more frequently between twenty and thirty years of age. It is usually associated with tuberculosis of other portions of the body, and primary tuberculous peritonitis is rare, if it ever occurs. The frequent association of tuberculous peritonitis with genital tuberculosis in both sexes,

pulmonary tuberculosis, tuberculous adenitis, or tuberculosis of some portion of the intestinal tract is an aid to its diagnosis, and in the presence of these forms of tuberculosis any abdominal symptoms or complications should suggest the possibility of tuberculous peritonitis. The coexistence of involvement of another serous cavity, especially the pleural cavity, is of great importance in diagnosis. In women it is frequently associated with underdevelopment of the genital organs and sterility. The occurrence of tuberculous peritonitis as a part of a general miliary tuberculosis will not be considered here. The disease occurs in three forms: the miliary, 68 per cent., the chronic adhesive, 27 per cent.; the chronic ulcerative, 4 per cent. Symptomatically we have the acute, the subacute, and the chronic types, the latter two usually merging into each other. The acute type may simulate acute appendicitis or intestinal strangulation, and the temperature may reach 103° and 104°. The subacute type with abdominal pain and tenderness, continued fever, distention, diarrhea, and relatively low leukocyte count may be confused with typhoid fever. In the subacute and chronic types the presence of fluid or tumor masses usually leads to the diagnosis, especially when there are multiple masses present. We have found that the presence of palpable nodules due to conglomerate tubercles on the peritoneum of the cul-de-sac, which are readily felt on rectal examination, has been of value in diagnosis, although in these cases metastatic new growths must be ruled out. In 4 of our cases these nodules were felt on rectal examination. Moderate distention, abdominal tenderness without muscle spasm, abdominal discomfort, anorexia, alternating constipation and diarrhea, irritability of the bladder, weakness, loss of weight, and sometimes vomiting may be prominent features; in fact, the symptoms are most varied, and this disease may simulate almost any intra-abdominal condition, as is evident by the variety of incorrect diagnoses made in this disease. The symptoms and signs due to the presence of excess of fluid may constitute the whole clinical picture. Pigmentation of the skin occurs in quite a percentage of the cases, and there is usually a rise of temperature which varies from a high continued fever to a slight evening elevation. Normal or even subnormal temperature may be present. Blood-pressure is usually low. A normal or slightly increased leukocyte count with relative lymphocytosis is usually present as in other forms of tuberculosis, and is a diagnostic aid.

The tuberculin tests are o limited value. We have had some interesting experiences with the von Pirquet test, in that in several of the cases a weakly positive test became strongly positive as the patient's condition improved, especially in the rapid improvement that sometimes follows a laparotomy. In one instance a negative von Pirquet test on admission of the patient made us doubt the presence of a tuberculous process. This patient was emaciated

and anemic, and there were multiple masses felt in the abdomen and on rectal examination nodular masses were felt in the cul-de-sac. The negative von Pirquet test made the diagnosis of malignancy very probable, although our first impression was that of tuberculosis. After several weeks of treatment, in which the patient's general condition improved, the von Pirquet test was repeated and found positive. This was absolutely diagnostic, and at operation extensive tuberculous involvement was found. This patient was evidently so overwhelmed with the infection when first observed that there was no reaction to tuberculin; but as improvement took place and the patient attained a resistance there was again a response to the tuberculin test. We have seen several very weakly positive von Pirquet tests in tuberculous peritonitis, and in three the test was absolutely negative The subcutaneous test is of value in the afebrile cases, but should be used with caution. When there is ascites it is sometimes difficult to differentiate from cirrhosis of the liver, especially since the two are often associated, the cirrhosis with ascites apparently predisposing to tuberculous infection of the peritoneum. The cytology and bacteriology of the fluid is not of much value in differentiating from other types of ascites, because tapping of the abdomen is dangerous in this condition, as the ascitic and adhesive processes are frequently combined and the danger of puncturing the intestine is a real danger. Tubercle bacilli are seldom found in the fluid. A lymphocytosis of the fluid is suggestive of tuberculosis, as is also the presence of a bloody fluid.   The fluid is usually straw-colored or bloody, and may be purulent in the chronic ulcerative form.   Encysted fluid in the midline, often mistaken for an ovarian cyst, and tumor due to rolled-up omentum lying transversely across the upper abdomen are frequently observed in the chronic forms. Multiple irregular masses often lead to the diagnosis of a malignant condition. It is interesting to note that in 2 of our cases the appendix had been removed previously, with diagnosis of chronic appendicitis, but without relief of symptoms.

The prognosis of tuberculous peritonitis is good. Oschner states that 50 per cent. are cured by medical treatment alone and that 50 per cent. of the remainder are cured by surgical intervention. Cases should be well for at least three years before pronounced cured, as there are many relapses within that time. The prognosis is affected unfavorably by the presence of active tuberculosis of the lungs or extensive intestinal tuberculosis. Persistent diarrhea usually signifies intestinal involvement.

Of the different forms of tuberculous peritonitis the chronic ulcerative caseating variety presents the least chance of recovery with either method of treatment. Collections of pus in the abdominal cavity or between coils of intestines, perforation, and fecal fistulæ are to be feared in this variety.

The history of tuberculous peritonitis is that it was at one time considered hopeless. This was followed by the surgical age in which all cases were operated, with a high percentage of reported cures, which, however, failed to stand the test of time. The pendulum swung back to where operation was considered by some as of no benefit, while others insisted on its value. Today there is an effort to select those cases which are best suited for so-called medical treatment and those in which surgical procedures are indicated. There is no doubt that in properly selected cases, laparotomy, under conditions which throw the least strain on the reserve strength of the patient, is followed by a much more rapid and marked primary improvement in the condition than under medical treatment alone, and that in cases that are apparently at a standstill or in which the process is actually extending, laparotomy frequently turns the tide and is followed by improvement. The medical treatment is always indicated, and operation should be merely an incident in the general plan of treatment. In patients who were not considered proper subjects for surgical treatment when first seen, and were treated medically until conditions were more favorable, we have repeatedly observed that the comparatively slow improvement under medical treatment was followed by rapid improvement after laparotomy, and that surgery deserves a place in the treatment of tuberculous peritonitis cannot be denied. The objection that the cures are not permanent and that recurrences occur is just as true of medical treatment. In properly selected cases the primary improvement is usually marked, but these patients must be kept under a careful régime until the danger of recurrence is past.

The treatment of tuberculous peritonitis should be similar to the treatment of tuberculosis elsewhere, in that it should be primarily the treatment of the patient's general condition and the treatment of the local condition is secondary, since complete surgical extirpation of the diseased area is impossible. There have been various theories as to the way in which simple laparotomy acts favorably in these cases. The most logical one seems to be that the good effects of laparotomy come from the resultant hyperemia from exposure of the peritoneum to the air. Nassauer reopened the abdomen three hours after operation for tuberculous peritonitis and observed a hyperemia of a degree which he says cannot be appreciated unless actually seen. Laparotomy in experimentally induced tuberculous peritonitis in rabbits is followed by a hyperemia of greater degree and longer duration than in rabbits without tuberculous peritonitis. This is due to the action of air on the peritoneum as it does not occur if the operation is done with the animal submerged in normal salt solution. It is this hyperemia that we aim to get in the use of tuberculin in the focal reaction. It is the foundation of Bier's hyperemia treatment of tuberculosis. Tuberculous lesions anywhere in the body are healed by encapsulation

with fibrous tissue. The lymphocytes play a part in the fight against tuberculosis analogous to the part played by the leukocytes in other infections. There is a zone of lymphocytes surrounding the tubercle and a relative lymphocytosis in the blood just as there is a zone of polymorphonuclear leukocytes around a pyogenic infection and a polymorphonuclear leukocytosis in the blood. In this hyperemia more blood and more lymphocytes are brought to a relatively chronic lesion, and in this way the natural processes of combating the tubercle bacilli and encapsulating them with fibrous tissue are aided. There is also an absorption of the products of growth of the tubercle bacilli as a result of this hyperemia which is equivalent to a dose of tuberculin. This is greatest in the acute cases and becomes less in the more chronic types. It is because of their absorption that laparotomy in the acute types may be actually harmful. That such absorption takes place is well shown in Case No, 15 of our series, in which the temperature rose sharply to 105° following simple laparotomy. This is equivalent to a large dose of tuberculin, and therefore is contra-indicated in the acute types of the disease in which the patient is already absorbing more than he can properly care for. For this reason patients with continuous fever above 99.5° or 100° should be treated conservatively until the process becomes more chronic. We hesitate to operate upon these cases for the same reason that we hesitate to give tuberculin to patients when the temperature is elevated. It is a different proposition from that in which a tuberculous lesion can be completely excised.

The best results surgically are obtained in the chronic types with little or no fever, and especially in the miliary form with ascites. The impression that the fibro-adhesive form is not amenable to surgical treatment has not been our experience, for the types so frequently overlap, the miliary form being present in one portion of the abdomen and the fibro-adhesive form in another, the one form apparently an advanced stage of the other, and a complete disappearance of both may occur after laparotomy.

Because of this overlapping of forms, on opening the abdomen if we encounter adhesions we lengthen the incision in an effort to get into the free peritoneal cavity, where we may find the miliary form. The operative procedure should be as simple as possible, consisting of laparotomy, with evacuation of fluid, if present, exposure of the peritoneum to the air, with a minimum of trauma and intra-abdominal manipulation, and closure of the incision without drainage. Intra-abdominal medication is useless. Extensive breaking up of adhesions and the use of drains predispose to fecal fistulæ and persistent sinuses, usually from secondary infection. The chronic adhesive form of tuberculous peritonitis is a healing process, and to break up these adhesions, unless for the purpose of relieving intestinal obstruction, is meddlesome surgery. The focus of infection should be removed only when it can be done with little manip-

ulation. The operative treatment is largely a local treatment and the patient should be in as good general condition as possible, and the operation should not be so severe as to tax the patient's resistance. It should be done under conditions that conserve to the greatest degree the strength of the patient, preferably under local or spinal anesthesia, preceded by the use of opiates.

The conservative or non-operative or so-called medical treatment with which the surgical treatment should always be combined consists of keeping the patient at rest in bed and outdoors and on as liberal a diet as possible. When the temperature comes down we give tuberculin, estimating the dose for each individual patient by the method that was developed at the Tuberculosis League in Pittsburgh. During the last two years we have been following Rollier's method of heliotherapy with good results. Although conditions in Pittsburgh are not as favorable for this form of treatment as are those in Switzerland, we feel that our results have been better since instituting this plan. Limited portions of the body are exposed daily for short periods to the direct rays of the sun, gradually increasing the surface and the time of exposure until the whole exposed body is well tanned. The head should be protected and the eyes shielded from the glare of the sun, and care should be exerted as to the rapidity in which the exposures are increased, judging this chiefly by the way the patient responds. Headaches and exhaustion are indications of improper reactions. The process of tanning should be gradual and sunburns should be avoided. By keeping the patient in the sun covered only by a sheet the tanning process takes place to a certain extent at times other than when the parts are directly exposed. These patients should be treated until all signs and symptoms of the disease have disappeared, and a similar régime should be followed as nearly as possible for at least six months after the patient is allowed to walk. The patient should be observed for at least three years, for the brilliant results of any treatment are much dimmed by the large percentage of cases that fail to stand the three-year test that is insisted upon as essential to a cure. The prognosis of localized tuberculosis in children under conservative treatment is always better than in adults, and the indications for operation are less in this as in other forms of surgical tuberculosis in these young patients. We have had no experience with the roentgen-ray treatment of this disease.

This paper is based on the analysis of 21 cases. Two left the hospital without operation, and in 1 case that died no autopsy was obtained. In the remaining 18 the clinical diagnosis was confirmed at operation or autopsy.

TREATMENT AND RESULTS. Of the 21 cases, 14 were operated on at the St. Francis Hospital and 2 had been operated elsewhere; 5 were not operated. Of the 5 cases that were not operated, 3 died in the hospital, 2 of them within two days after admission, and the

other 1 in two and a half weeks. One case refused operation and left the hospital in three weeks unimproved. The other case was of the acute type and simulated typhoid fever. This patient was not considered as the type for operation, and was treated conservatively and left the hospital improved. Of the 2 cases operated on at other hospitals and admitted later to the St. Francis Hospital, 1 left improved and the other unimproved. This patient refused to remain longer than three weeks. Of the 14 cases operated on at the St. Francis Hospital 1 died ten weeks after operation. This patient had tuberculous pleurisy and the chronic adhesive type of tuberculous peritonitis. The von Pirquet reaction was negative. Adhesions were so dense that a very limited portion of the abdomen was exposed. The patient became greatly emaciated before death. The differential count in this case one week before operation showed 3.7 per cent. small mononuclears. We believe that this is important and that a low lymphocyte count indicates a low resistance. The remaining 13 cases were discharged improved, with temperature normal or with only an occasional rise in the evening, and a diminution in size or a disappearance of palpable masses and with no evidence of reaccumulation of fluid, and with an improvement in the patient's general condition. In 3 of these cases differential counts were made before and after operation, and all of them showed a marked increase in lymphocytes after improvement. Most of the cases showed a marked primary improvement soon after operation. The average duration of treatment in the hospital before operation was two weeks and after operation eight and a half weeks. One case had been treated for five weeks at the St. Francis Hospital five months beforehand with diagnosis of typhoid fever (?). On second admission diagnosis of tuberculous peritonitis was made and confirmed at operation. Another case simulated typhoid fever until the clinical diagnosis of tuberculous peritonitis was made by finding nodules on the peritoneum of the cul-de-sac. The fluid from the peritoneal cavity was examined in 2 cases, the one showing a specific gravity of 1022, and contained 91 per cent. lymphocytes. The other one showed 69 per cent. lymphocytes. No tubercule bacilli could be demonstrated in smears or on injection of guinea-pig.

END RESULTS. Letters were sent to 17 patients. Three of the letters were returned unopened. No replies were received in 8. Five reported as well. One of these was operated six years ago and one three years ago. The remaining 3 were operated on in the last two years. One of the cases, not operated, reported as improved, but has occasional attacks of abdominal discomfort.

ANALYSIS OF CASES. The oldest patient was sixty-three and the youngest two years of age. Eleven were between twenty and thirty years. There were 11 females and 10 males. There was 1 case of the chronic ulcerative type, 5 of the chronic adhesive, and the remainder the miliary with or without fluid and adhesions. In

4 of this series there is a note of palpable nodules in cul de sac. Six patients were recorded as well nourished. The rest were poorly nourished or emaciated. In 17 of the cases there is record of one or more leukocyte counts. The highest count was 16,000. This was in the 1 case of the chronic ulcerative type with pus formation. The lowest count was 5150. This patient died without operation. No differential count was made. Average white cell count in the series was 9990. The hemoglobin was recorded in 15 cases, the highest being 90 per cent., the lowest 52 per cent., and the average 72 per cent. Differential counts were recorded in 11 cases, with an average of 28.3 per cent. mononuclears. There was a differential count on only one of the fatal cases. This patient died ten weeks after operation, and was the only operative fatality. The count was made one week before operation, and showed 3.7 per cent. small mononuclears and 14.9 large mononuclears. Differential counts before and after operation were recorded in only 3 cases. In 1 there were 9 per cent. small mononuclears and 11.5 per cent of large mono-nuclears three weeks before operation, while two and a half months after operation there were 27 per cent. of small mononuclears and 5 per cent. of large. In another there were $17\frac{1}{2}$ per cent. of small and and $7\frac{1}{2}$ per cent. of large mononuclears two days before operation, and one month after operation there were 33 per cent. of small, and 5 per cent. of large mononuclears. In the other case seven days before operation there were 20 per cent. of small mononuclears and 10 per cent. of large, while thirteen days after operation the small mononuclears were 30 per cent. The von Pirquet test was done in 9 cases. Six were positive and 3 were negative. One of these became positive later. The Wassermann test was done in 3 cases and was negative in all of them. There were no cases of primary tuberculous peritonitis, for other organs were found involved in all of the cases, namely:

Glands in 8; adnexa and lung in 1; lungs in 3; lungs and testicle in 1; lungs and pleura in 3; pleura in 3; meninges in 1. Of the 6 cases with pleural involvement, 4 had effusion.

In 9 of the 14 patients no organs were removed at operation. In the remainder the tubes or the appendix were removed. Drainage was used in 2 cases. In one of these, the ulcerative type, a fecal fistula followed. In the 2 patients operated elsewhere there were sinuses, but it is not known whether drainage was used. In 3 of the cases in which no drainage was used a sinus appeared later and persisted for a variable length of time.

REVIEWS

Eye, Ear, Nose and Throat. By Howard Charles Ballenger, M.D., Professor of Oto-Laryngology in the Chicago Eye, Ear, Nose and Throat College, etc., and A. G. Wippern, M.D., Attending Oculist and Aurist to St. Elizabeth's Hospital, Chicago, etc. New second edition, thoroughly revised. Pp. 524. Illustrated with 180 engravings and 8 colored plates. Philadelphia and New York: Lea & Febiger, 1917.

This little text-book on the eye, ear, nose and throat, written by authors whose names in themselves are a guarantee of excellency, now appears in its second edition. It is a small concise work written for the use of students and general practitioners. In this edition there has been a radical revision of the greater part of the book; enlarging and improving the chapters on anatomy and methods of examining the ear and adding chapters on malformations of the external nose and the technic for tonsillectomy. The book is well balanced, covering the whole field of the eye, ear, nose and throat and giving sufficient detail concerning the more common diseases and operations for a fairly comprehensive knowledge of the matter. We regret, however, that more space has not been given to the section on the ear, and especially to the modern method of examining the static labyrinth and its relation to cerebellar disease. Also the pathology is disappointing, being frequently not mentioned and generally unreliable. As a practical treatise, however, we heartily recommend this book as a useful addition to the general practitioner's library, and the descriptions of the technic more of the common operations will be a great help to the beginner in this specialty. The illustrations are above the usual, and there is appended a formulary for the ear, nose and throat.

G. B. W.

Modern Medicine and Some Modern Remedies. Practical Notes for the General Practitioner. By Thomas Bodley Scott. First edition. Pp. 159. New York: Paul B. Hoeber.

The book consists of four essays upon the following subjects: disorders of the heart, arteriosclerosis, therapeutic speculations, and

doubts, and chronic bronchitis and bronchial asthma. It is of special interest, as it is a publication of facts as observed by a general practitioner. It also sets forth the difficulties of a general practitioner in handling heart and arteriosclerotic cases.

In speaking of valvular disease as results of an infection process, there is a failure to mention tonsillitis and chorea as important etiological factors. Syphilis, especially in America, plays a greater role in the etiology of aortic valvular disease than the author brings forth.

The presclerotic period is well exemplified by the author as well as the important use of the sphygmomanometer and the simple management of these cases.

The results of internal secretion medication are well drawn and practical. The use of autogenous vaccines, grown anaërobically, in bronchial asthma, with their results is well shown and there is no doubt of their good effect in riding the patient of his severe bronchitis after which the asthma apparently clears up.

The book is well written and should serve its purpose in stimulating other general practitioners to tabulate and hand down many useful points observed at the bedside.   T. K.

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PRINCIPLES OF DIAGNOSIS AND TREATMENT IN HEART AFFECTIONS. By SIR JAMES MACKENZIE, M.D., F.R.S., F.R.C.P., LL.D. Ab. and Ed., F.R.C.P.I. (Hon.), Physician to the London Hospital (in charge of the Cardiac Department), Consulting Physician to the Victoria Hospital, Burnley. Pp. 264. London: Henry Frowde, Oxford University Press. Hodder & Stoughton, Warwick Square, E. C.

THIS book contains a series of lectures which were to have been delivered to the postgraduate students and workers at the Cardiac Department of the London Hospital. The outbreak of the war having prevented their delivery the author presents them in book form.

The purpose of the lectures is not only to give the essential features concerning heart failure in a manner useful to the practitioner, but also to offer a better insight into clinical medicine and thus stimulate research in this line. In regard to the evidences produced by mechanical aids, as the polygraph and electrocardiograph, the reader is referred to the author's book on *Diseases of the Heart*.

The first chapter deals with the subject of medical research and shows how the progress of medicine has been and will be delayed until the practitioner becomes more of an investigator. The value

of close observation and carefully kept records the author supports as the essential features for the foundation of clinical research. Further emphasis is laid upon the recognition and significance of the patient's sensations in order to establish an early diagnosis and satisfactory treatment.

The author next discusses heart failure along practical lines, mentioning the functional properties of the heart muscle, its action in rest and in activity, exhaustion of reserve force, and early subjective sensations, etc. The patient's sensations and the production of symptoms are next considered, the chapters on breathlessness, syncope, and objective signs of heart failure containing much of use to the physician, who, after some practical experience, wishes to review the subject. The chapter on angina pectoris, viewed as an expression of exhaustion of the heart muscle, gives a basis for sound prognosis and rational treatment. Such terms as "pseudo-angina," or "mock angina," the author suggests are merely used to "cloak our ignorance by a vain and empiric nomenclature."

The true significance of murmurs—physiological, functional, and organic—is very clearly presented and the observations and conclusions based on many years of experience cannot fail to be of material use to the general practitioner. Just how frequently these murmurs are misunderstood is revealed by numerous instances cited by the author. Under heart irregularities he offers a good classification into the "youthful" and "adult" types, and again calls attention to the failure of the practitioner to grasp the real significance of these irregularities.

He speaks of the "doctrine of back pressure, with its attendant verbiage of compensation and decompensation," as having "blinded the profession to the real facts for the past sixty years," and shows how a clear understanding of auricular fibrillation furnishes a true knowledge of what heart failure really means. His chapter on blood-pressure is a conservative one and sounds a wholesome warning in regard to the too free offering of an opinion based on blood-pressure readings alone. Many useful suggestions are given under prognosis and treatment; and while the latter might not be considered by some as being particularly comprehensive, it is, above all, practical and sound.

The author's views are refreshing in regard to the much flaunted Nauheim baths, the reputation of which, he concludes, rests more on "brazen advertisements, financial interests, and slavish tributes of other spas than on an intelligent appreciation and application of the principles of therapeutics."

The usefulness of the book may be appreciated when one considers its foundation, which is based on many years of close observation and careful study, in which recent advances find their place and to which personal views are freely contributed.   A. H. H.

VENESECTION: A BRIEF SUMMARY OF THE PRACTICAL VALUE OF VENESECTION IN DISEASE. By WALTER FOREST DUTTON, M.D. First edition. Pp. 220; 3 full-page plates. Philadelphia: F. A. Davis Company.

A BRIEF, yet a complete, review of the history of blood-letting from earliest Egyptian restrictions of surgical procedure, 2500 B.C. until the present time. The evolution from the crude methods of that time, through the different European periods, as advocated by the fathers of medicine as Hippocrates, Galen, Belsur and others. It is told in a most interesting and helpful manner.

The chapter on hematology is a text-book description and prepares the way for a brief and concise discussion of the etiological and therapeutic benefits of venesection. It is arranged systematically, with indications, technic and results to be obtained.

The author still advises cutting down on the vein. I have found it more practical, quicker, and less disagreeable to the patient to use a No. 18 needle to which is attached a three way stop cock. To one of the ways a tube leading to a vacuum bottle, as in an aspirating outfit. To the other way a sterile funnel is attached, so that in toxic conditions normal saline can be introduced if desired. I have had no trouble in securing 20 to 30 ounces of blood and in less time than by "breathing the vein."

The chapters upon heart diseases and hypertonia vasorum cerebri are especially well taken. The author quotes frequently most of the authorities, and all the material is especially well chosen. Many of the vague symptoms are explained on a substantial pathological basis. The book is most helpful to a busy practitioner.   T. K.

CLINICAL DISORDERS OF THE HEART BEAT: A HAND-BOOK FOR PRACTITIONERS AND STUDENTS. By THOMAS LEWIS, M.D., D.Sc., F.R.C.P., Assistant Physician, University Hospital College. Third edition. Pp. 116; 54 illustrations. New York: Paul B. Hoeber.

A REPETITION of the two previous editions, with the addition of eleven pages to the chapter on auricular flutter, also alterations and changes in diagnosis. The book gives a clear cut and concise description of the important cardiac irregularities recognizable without the aid of the polygraph or the electrocardiograph. It is invaluable to the student who wishes to understand cardiac irregularities from the modern conceptions. The simplicity in which it is written is a valuable asset. The chapters upon heart-block and auricular flutter are of special interest.   T. K.

SURGICAL NURSING AND TECHNIC. By CHARLES P. CHILDE, B.A.,
F.R.C.S., Eng., Lieut.-Colonel, Royal Army Medical Corps
(Territorial); Senior Surgeon, Royal Portsmouth Hospital;
Medical Officer in charge of the Surgical Division, 5th Southern
General Hospital, Portsmouth. Pp. 229, 9 plates. New York:
William Wood & Co.

THE title of this small treatise has been changed in issuing it
in a second edition. The general make-up, however, remains the
same, except for many changes brought about by the military
aspect of English nursing since the onset of the war. The author
takes up antisepsis and asepsis briefly, follows this by three excellent
chapters on the care of the patient before, during, and after opera-
tion from the stand-point of the nurse. There is a chapter devoted
to the selection of instruments and one upon operations in private
houses. The final chapter is devoted to a discussion of nursing in
military hospitals. A rather interesting feature of the book is the
way the author takes up the cudgels for the betterment of the
economic conditions of the nurse in training. The volume is an
interesting book for the surgical nurse.   P. F. W.

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PREVENTIVE MEDICINE AND HYGIENE. By MILTON J. ROSENAU,
Professor of Preventive Medicine and Hygiene, Harvard; Director
of the School for Health Officers of Harvard University and
Massachusetts Institute of Technology; formerly Director of the
Hygienic Laboratory, U. S. Public Health Service, etc. Second
edition. Pp. 1286; 172 illustrations. New York and London:
D. Appleton & Co.

SUCH an exhaustive treatise as this one from Dr. Rosenau is
baffling to review. Each subdivision is an epitome of the best and
most modern scientific though upon the subject treated, and carries
with it the authoritativeness that can come only from those of such
large experience as the author and his colaborators. This review
consequently attempts merely to indicate the wide extent of the
work and to recommend it to all those interested in any branch of the
subject.
   As was stated in the preface to the first edition, "the work is
planned to include those field of the medical and related sciences
which form the foundation of public-health work," and it is the only
American book covering this wide range. The first section deals
with the prevention of the communicable diseases, and the author's
presentation of this subject is unique in that the diseases are taken
up in accordance with their mode of transference, as is suggested,
for instance, by such chapter headings as "diseases having specific

or special prophylactic measures," "diseases spread largely through the alvine discharges," "insect-borne diseases," etc. In this way, from the preventionist's view-point, the emphysis is placed where it belongs.

The second section deals with immunity, heredity, and eugenics in a very comprehensive and enlightening manner. Foods, air, soil, and water respectively are discussed in the following divisions. The sections upon sewage and refuse disposal are presented by George C. Whipple, and are sufficiently detailed to be of invaluable aid to those engaged in such sanitary problems. Vital statistics is covered by John W. Trask. The division devoted to industrial hygiene and diseases of occupation is a satisfactory, but very limited, presentation of that very interesting group of disease conditions and of the known means of preventing them. Other parts of the work deal with schools, disinfection, and military hygiene.

Among the subjects which are new to this edition are the Schick reaction, the Bang method of suppressing bovine tuberculosis, emetin, certain insecticidal agents, standardization of bacterial vaccines, sodium fluoride, hydrofluoric acid, carbon dioxide in alveolar air, sanitary significance of odors, etc.   T. G. M.

THE PRACTICE OF UROLOGY. A SURGICAL TREATISE ON GENITO-URINARY DISEASES, INCLUDING SYPHILIS. By CHARLES H. CHETWOOD, M.D., LL.D., F.A.C.S., Professor of Genito-urinary Surgery, New York Polyclinic. Second edition. Pp. 825; 325 illustrations. New York: William Wood & Co.

THE second edition of Chetwood's *urology*, appearing in three years after the first, deserves and will undoubtedly be received with the favor which characterized its predecessor. The frontispiece, a collection of fifteen figures from a cinematograph film depicting nephrolithotomy and nephrectomy, is a popular creation of the hour, but it is doubtful if much real surgery will ever be taught by the spectacular method of moving pictures. As we had occasion to remark previously, the attention given by the author to bacterin, or "vaccine," therapy in the chapter on serodiagnosis and sero-therapy is especially commendable, although we would take exception to any description or recommendation conducive to a populari-zation of "phylacogens." Criticism might be offered that it would be advisable to include the working technic of the complement-fixation tests for syphilis and gonorrhea.

The chapters are well proportioned and noteworthy in the new edition, are innovations relative to the teaching of cystoscopy, also the additions of practical advantage in the operative technic and the new section on local anesthesia. More attention has been given to the technic of administration of salvarsan and neosalvarsan.

In the chapter on functional renal diagnosis the author's preference for the phenolsulphonephthalein test and the estimation of urea volume of the urine is noted. We cannot agree that the indigocarmin test is "less accurate," and contend that even though only 25 per cent. of the amount injected is eliminated by the kidneys, that this offers no disadvantage to its practicability and reliability. Exception must also be taken to the author's technic of employment of this test. Insufficient attention is accorded the renal tests of retention, especially total non-protein nitrogen and the blood-urea nitrogen.

The final 107 pages are devoted to a consideration of syphilis, and the subject is extremely well covered in this space. Some of the illustrations, particularly the borrowed ones, are scarcely in keeping with the high standard of the great majority.

A commendable feature, enhancing the work as a text-book for students, is the use of heavy-face type for important phrases. The general appearance of the book, the excellence of the type employed, and the binding distinguish the production and the reputation of the publishers.   B. A. T.

THE NEWER METHODS OF BLOOD AND URINE CHEMISTRY. By R. B. H. GRADWOHL, M.D., Director of the Pasteur Institute of St. Louis and the Gradwohl Biological Laboratories, St. Louis, and A. J. BLAIVAS, Assistant in the same. Pp. 240; 65 illustrations and 4 colored plates. St. Louis: C. V. Mosby Company, 1917.

THE purpose of the authors has been to collect into a compact book the larger part of the information on the subject that has appeared in the various journals during the past three or four years. This they have succeeded in doing to the advantage of the man engaged in laboratory investigation. The book is divided into three parts: (I) Technic of Blood Chemistry; (II) Chemical Analysis of Urine; (III) Blood Findings and Their Interpretation. It is well illustrated, easily read, and has both a subject and author index. On page 108 the "benzine" test for blood should read the "benzidine" test; the same error occurs in the subject index.

                                              H. E. D.

FOOD POISONING. By EDWIN OAKES JORDON, Chairman of the Department of Hygiene and Bacteriology, University of Chicago. Pp. 107; 11 illustrations. Chicago: University of Chicago Press, 1917.

IN a brief, simple, and entertaining manner the author summarizes and discusses food poisons so frequently met with in

every-day life and yet so imperfectly and indefinitely understood.
He estimates 1500 to 20,000 cases of food poisonings each year
in the United States. The discussion includes (1) sensitization to
protein foods, (2) poisonous plants and animals, (3) mineral or
organic poisons added to food, (4) food-borne pathological bacteria,
(5) animal parasites, (6) poisonous products formed in food by
bacteria, (7) poisons of obscure nature, (8) deficiency in some
elements of foodstuffs causing disease.

It is a clear, concise summary of our present knowledge of poison-
ing through foods handled in a semitechnical manner, clearly
demonstrating the great need of further and more thorough investi-
gation upon foods and poisoning thereby. The book is of value
to the medical profession as well as to the general public.

                                                        J. D.

PROGRESS

OF

MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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The Effect of Unilateral Extraction of the Intercostal Nerves upon the Lungs and its Tuberculous Disease.—WARSTAT (*Deutsch. Ztschr. f. Chir.*, 1917, cxxxviii) performed experiments on rabbits to determine the effect of the paralyzing of the intercostal nerves on the movements of the corresponding lung. Through a longitudinal incision at the external border of the erector spinæ muscle he exposed, with local anesthesia, the first eleven intercostal nerves and divided them after separating them from the pleura. This was done distal to the giving off of the dorsal branch which supplies the back muscles. The distal portion of the intercostal nerve was removed by tearing it out, neurexairesis. The twelfth intercostal nerve was not removed because it did not innervate the respiratory muscles of the chest wall. The unilateral exclusion of breast movements by means of so paralyzing the intercostal nerves, so quieted and collapsed the corresponding lung, that it must favorably affect, if tried, a tuberculous process in the lung and promote its healing. He did a similar operation on two patients with lung tuberculosis. It is suitable for use in man because the operation is simple and secondary complications need not be feared.

The Treatment of Bony Defects of the Lower Jaw.—McWILLIAMS (*Ann. Surg.*, 1917, lxv, 283) is convinced that no surgical lesion is generally so badly treated as infection and osteomyelitis of the inferior maxilla. This is due in the first place to timidity and ignorance on the part of the dentist who sees these patients in the beginning. His ill-advised attempts to save abscessed teeth lead to more or less wide spread necrosis of the jaw. Secondly, the general surgeon frequently attacks the necrosed area with the curet and chisel with too much vigor, thus increasing the necrosis by trauma. He reports 3 new cases and a second grafting operation on one of 2 cases previously reported. The main lessons to be learned from these patients are as follows:

Infection from the mouth at the time of making the grafts is absolutely fatal to the entire graft. A part only of the graft may necrose away. No grafting should be made in the presence of a sinus or into a granulating cavity. Grafting should be made any number of times until a successful result is obtained. In view of the great liability of bone grafts into the lower jaw to infection, McWilliams is inclined in his next cases to use costal cartilage as grafting material, since this is more viable than bony grafts and is not so liable to become infected. Absolute immobility of the lower jaw is a *sine qua non* to a successful result. Wiring the teeth proved more successful than splints. It should be maintained for three or four months after the grafting. The inlaying of the graft (always with its periosteum) into grooves cut in the sides of the fragment would seem to be a more scientific procedure than end-to-end grafting. Metal sutures had best not be used, owing to their liability to invite infection.

The Prognostic and Therapeutic Significance of Skeletal Metastases in Carcinoma of the Breast.—LEVIN (*Ann. Surg.*, 1917, lxv, 326) says that in the overwhelming majority of all cases of cancer of the breast the best surgical treatment do not completely eradicate the disease, but only prolong life. The correct treatment of carcinoma of the breast, complicated with skeletal metastases consists in the operative removal of the gross tumor mass combined with radium and roentgenotherapy. The radiations in a postoperative case of carcinoma of the breast should not be given only over the operative field and over the chest wall, which is the procedure generally adopted today, but should include, if not the whole skeleton, at least the spine and heads of both femurs. Moreover this combination of surgery and radiotherapy should be the method of choice in all advanced cases of carcinoma of the breast, even when there is not yet evidence of skeletal metastases. One of the important effects of radium and roentgenotherapy consists in the formation of an extensive connective-tissue stroma, surrounding and compressing the tumor cells. In skeletal metastases this stroma is transformed into bone. It is thus *a priori* self-evident that the radiotherapy must enchance the results of the attempts at cure produced by nature.

Renal Tuberculosis.—RYTINA (*Ann. Surg.*, 1917, lxv, 346) reports a study of 3 cases of renal tuberculosis. The first shows that an almost generalized tuberculosis of the genito-urinary tract may be present without the production of any grave symptoms and that following radical removal of the chief foci, rapid, spontaneous retrogression of the disease in the remaining organs can take place. The second case proves the erroneousness of the teaching of some surgeons that tuberculosis of the kidney can be diagnosed by inspection and palpation of the organ at the time of operation. Indeed, bisection of the kidney from pole to pole may fail to reveal the seat of an extensive tuberculous process. This point is worthy of emphasis, as Rytina has seen, in the last few years, several cases of renal tuberculosis which showed no evidence of its existence upon the surface of the kidney, but on section and examination of its interior a most advanced tuberculous condition. The moral of this is, that the diagnosis should be made prior to operation by the

employment of the cystoscope, ureter catheterization and functional tests, and once having determined the diagnosis, its removal should be resorted to, irrespective of its normal surface appearance at the time of operation. The third case indicates that an entire kidney may be destroyed by tuberculosis and exist for years without producing any renal symptoms or change in the general physical well-being of the individual. This case also shows the advantage of kidney functional tests in surgical renal conditions and at the same time that it is not fool-proof.

The Carrel Method of Wound Sterilization.—SHERMAN (*Surg., Gynec. and Obst.*, 1917, xxiv, 255) says that if it is necessary to amputate for loss of substance, a chop or guillotine aperiosteal operation is the method of choice; this to be followed by Carrel's method of wound sterilization. According to Tuffier 80 per cent. of the amputations are due to infection and 20 per cent. to destruction of tissue. The original Dakin solution contained: 140 grams dry sodium carbonate dissolved in 10 liters of tap water, to which 200 grams chloride of lime (chlorinated lime) is added and 40 grams boric acid. The detailed preparation is given of the solution as now used (technic of Dufresne). Many of the so-called Dakin solutions are not prepared in accordance with the formula of the name they bear and as a result the solution has been condemned where some other solution has been used in the name of Dakin. To be successful one must follow the technic of Carrel. Dakin's solution represents but 20 per cent. of the cure and the technic of Carrel represents 80 per cent. It should never be forgotten that the solution must not be heated. It should never be applied or used in the eye or intravenously, because of its hemolytic action. It should be kept in a cool place, free from exposure to light. It should never come in contact with alcohol. It has been demonstrated that the great majority of wounds can be closed by suture and without suppuration. The stay of the wounded in the hospital and period of convalescence is greatly shortened and many now leave in four to six weeks, who would have required treatment from three to six months under former method. All complications such as atrophies, ankylosis, adhesions, septicemia and amputations are minimized; the mortality rate is also greatly reduced. Sherman concludes that infection can be aborted if the treatment is begun within the first twenty-four hours. Suppuration, when well established, can be controlled if the focus can be reached. The success of the treatment is dependent upon the perfection of the Carrel technic and the acceptance of all the details. The effect of Dakin's solution is entirely local; there being no danger of toxemia from absorption, regardless of the amount used. Carrel's technic, using Dakin's solution, is a specific against infection of wounds.

The Etiology and Treatment of Varicose Ulcer of the Leg.—HOMANS (*Surg., Gynec. and Obst.*, 1917, xxiv, 300) says that in summing up the treatment of chronic leg ulcers not obviously of varicose origin, it may be said that when well defined, or of any considerable size, and presenting a hard scar base, they are best treated by radical excision and skin graft. When they are a manifestation of a previous general infection of the subcutaneous tissues (and local veins) of the lower leg

they should be conservatively treated by measures tending to improve the surface circulation. Varicose ulcers take origin in profound nutritional disturbances attributable to varicose veins, but their incidence and development are profoundly influenced by trauma and infection. Varicose ulcers arising from the familiar type of surface varix run a chronic course and are generally healed by adequate removal of varicose veins. Varicose ulcers dependent upon postphlebitic varix are characteristically different from the first class in appearance, rapid in development, always intractable to palliative treatment, generally incurable by the removal of varicose veins alone, and must be excised to be cured. The lower leg, the seat of phlebitis, must be most carefully dissected, and every means should be employed to improve, during a protracted convalescence, the circulatory conditions in the leg. Chronic ulcers originating in trauma and infection should, if well defined, be excised and grafted.

A Substitute for Joint Ligaments.—STEINMANN (*Zentralbl. f. Chir.,* 1916, xliii, 979) refers to Katzenstein's case in which he substituted for a torn tibionavicular ligament, a free, transplanted, doubled periosteal flap, and thus overcame a traumatic flat-foot. Momberg, because, of the weakness of the periosteum, substituted a strip of the fascia lata. Steinmann obtained the Katzenstein advantage of intimate adhesion of the periosteum at the site of attachment and overcame the disadvantage of the weakness of the periosteum by taking with the periosteum a thin layer of bone. A twenty-five-year-old man, in March, 1914, tore the internal lateral ligament of the right knee. In extension of the knee, the leg could be bent outward 10 to 15 degrees. The patient experienced marked laxity of the joint on certain movements. On May 19, 1916, through a longitudinal incision, he exposed the lower end of the femur, joint, and upper end of the tibia. From the upper third of the tibia, at its inner angle, a periosteum bone flap was chiselled off, about 8 cm. long, 1 cm. wide and 3 mm. thick. This was turned upward, the upper end laid under the periosteum of the internal condyle of the femur, and fixed to it by a few sutures. This turned the bony layer of the flap outward. After three weeks' fixation, movements of the knee were begun and after six weeks, the patient got up on his feet. August 3, 1914, owing to the beginning of the war, he left the hospital, with flexion of the knee of about 90 degrees. There was no effusion in the joint, and the leg could no longer be bent outward with the knee in extension. The roentgen ray showed a shadow of the bony layer in the new ligament.

Two Cases of Fracture of the Neck of the Femur in Children.— WHITBECK (*Am. Jour. Orthop. Surg.,* 1917, xv, 17) says that the principles upon which the treatment of a fracture of the femoral neck should be based are: (1) The immediate and complete reduction of the deformity, no matter of what type. (2) Effectual means of fixation, to allow union to take place. This principle is best exemplified in the abduction method of Whitman. It applies not only to complete but also to incomplete or impacted fractures, and it is important to emphasize this fact. The results of this treatment have been shown to be most satisfactory; not only has a complete, or nearly complete, ana-

tomical restoration of the break in continuity been effected, and firm union produced, but the accompanying complete functional restoration resulted. Moreover, the danger of bed-sores and hypostatic pneumonia, which cause death in so many cases treated by traction, is well met by the abduction method. The retention in plaster renders it practical to turn the patient from side to side for bathing, and raising the head and turning from side to side at intervals drains the chest.

THERAPEUTICS

UNDER THE CHARGE OF

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Modern Methods of Blood Transfusion.—LEWISOHN (*Jour. Am. Med. Assn.*, 1917, lxviii, 826) found that 0.2 per cent. instead of 1 per cent. is the percentage of sodium citrate and blood required for the safe prevention of coagulation. Such a mixture prevents coagulation of the blood outside the body for from two to three days; 5 gm. of sodium citrate can be introduced safely into an adult. Larger amounts are extremely toxic. He rarely transfuses more than 1000 c.c. of blood, which would represent 2 gm. of sodium citrate. However, even a transfusion of 1500 c.c. of blood would require only 3 gm. of sodium citrate, a perfectly safe dosage. The introduction of citrated blood causes a temporary shortening of the coagulation time of the recipient's blood. The coagulation time returns to its previous level usually in less than twenty-four hours. The author describes the technic of transfusion by the citrate method and emphasizes the importance of preliminary tests of the donor blood. The following important facts also ought to be kept in mind in connection with this question: Donors cannot be used a second time for the same patient without another test as to hemolysis and agglutination. Blood relatives (parents and children, brothers, etc.) have to be tested just as thoroughly as strangers, as their blood often is very incompatible in spite of their near blood relationship.

The Results of Treatment in Hodgkin's Disease.—YATES and BUNTING (*Jour. Am. Med. Assn.*, 1917, lxviii, 747) summarize their clinical experience in treating 63 cases of undoubted Hodgkin's disease over a period of eight years. They believe that Hodgkin's disease is due to an infection of low virulence but imitates tuberculosis and certain malignant neoplasms especially carcinoma in many details. They advocate the radical surgical extirpation of all involved tissue possible, followed immediately by intensive roentgen-ray therapy. Before resorting to radical operation it is important to determine and eliminate the portals of entry of the infection, such as diseased tonsils,

teeth, accessory sinuses, etc. It is possible by these means to reduce the danger of local recurrences and when recurrences do occur they are usually late and assume a more chronic type of lesion. If extirpation is not to be complete the authors believe it should not be attempted. They have seen hopeless dissemination follow excision for diagnosis and believe that such test excisions should be made only exceptionally. The authors have found the use of an immune serum is distinct value although they cannot offer proof that the diphtheroid bacillus described by them is the actual cause of the disease. Patients who tolerate the serum seem to improve more rapidly and to receive more permanent benefit than those not receiving serum treatment. Arsenic is without specific and lasting value in any form yet available from Fowler's solution to salvarsan. Fresh air, sunshine and proper feeding are infinitely superior to any drugs when there is indication for tonics. With regard to results the authors conservatively decline to give exact figures but they believe that as their experience increases and methods of treatment improve greater benefits are being obtained. They are of the opinion that in about 20 per cent. of all cases recovery is a possibility. By recovery is meant freedom of signs and symptoms of the disease for a period of five years. Earlier diagnosis and the recognition that Hodgkin's disease, if treated promptly and radically, is curable would raise this percentage materially.

The Treatment of Hodgkin's Disease.—HOLDING and BROWN (*Jour. Am. Med. Assn.*, 1917, lxviii, 701) report 18 cases of Hodgkin's disease in which the diagnosis was established by microscopic examination. These cases were all fully developed with lesions generalized throughout the body. The claims of a specific diphtheroid organism have not been proved, in fact, have been disproved by Lorrey, yet their study seems to point to an infectious origin of the disease. The treatment of Hodgkin's disease is extremely unsatisfactory both in results obtained and methods employed. Perhaps this is to be expected in a disease, the cause of which is unknown, and which on microscopic examination of involved tissues in its early stages is extremely difficult to differentiate from lymphosarcoma, lymphoma, thymoma, and the other adenopathies of lymphoid origin. No specific or constitutional method of treatment has been established. The modern methods advised are essentially the same as those employed for malignant tumors, complete excision and diagnosis by microscopic section in the earliest stages while the lesion is restricted to a single locus followed by prophylactic roentgen treatment, together with the searching out and the elimination of all possible foci of infection. The authors feel that particular emphasis should be laid on the necessity of extensive general roentgen treatment in all of these cases immediately after the diagnosis is established. The surgical removal is only local in its action, and constitutes more or less of a shock and drain on the patients' vital resources. The roentgen rays should be given over all lymphatic structures of the body, including the mediastinal and abdominal lymph nodes, thus giving us a general action which in proper dosages they have invariably found to improve the patient's general physical condition instead of weakening him as the extensive surgical operations did in the fully developed stages of the disease.

It was noticeable that better results were obtained when treatment was instituted in the early stages of the disease, when lesions were confined to one side of the neck. It is quite probable that if patients in whom the lesion was confined to the tonsil or to a few glands of the neck presented themselves for treatment, they might be cured by complete tonsillectomy and excision followed by postoperative roentgen treatment; certainly these methods should be given a thorough trial in cases in the incipient stages of the disease. The authors are of the opinion that radium will produce fully as good results as the roentgen rays in Hodgkin's disease. The results obtained by various methods of treatment over a period of three years' observation are summarized. The authors note that of the thousands of patients treated there are only two authentic cases in which the patients are reported symptom-free after five years.

The Diagnosis and Serum Treatment of Anterior Poliomyelitis.— ZINGHER (*Jour. Am. Med. Assn.*, 1917, lxviii, 817) gives a summary of cases of poliomyelitis treated with immune and normal human serum. It is interesting to see that of 54 preparalytic cases treated with immune serum, 44 remained free from paralysis, while of the 10 who developed some form of paralysis, 5 made a complete final recovery. The results with normal serum seem to be very favorable, but the number of cases treated in the preparalytic stage of the disease is too small, and a larger series of cases should first be treated before final deductions are made. The author says it is difficult to state how many of the patients treated with serum would have remained free from paralysis without serum treatment. It seemed, however, that the action of serum in poliomyelitis is beneficial; that the use of serum from recent immune donors is preferable to normal serum, but that human serum is indicated in the treatment of the acute stages, especially in the preparalytic period of the disease. When carefully observed and controlled, the treatment is harmless. A distinct reaction follows in some of the cases after the first dose; the reaction is less marked after the second, and little, if any, is noted after the third injection of serum. Two groups of cases seemed to give an unfavorable prognosis even in the earlier stages of the disease. One was the fulminating bulbar type with a rapidly progressive involvement of the respiratory center. The second type was a rapidly developing spinal paralytic form. In the latter cases, which were treated after the paralysis had already made a distinct headway and was beginning to involve the muscles of respiration, the serum showed possibly in a certain proportion of cases an inhibitory effect on further progress, which resulted in a saving of life. It is difficult to forecast, however, what the natural result of the disease would have been in these cases. Control patients without serum, in whom the muscles of respiration were involved at the time the patients came under observation, have also recovered. It seemed, however, that a larger number of serum-treated patients of the same degree of severity had remained alive than would have without the use of serum. No very definite judgment of the value of serum can be based on the results obtained in these cases. Yet, as a possible life-saving procedure, the author would continue to use the serum even in these cases and in the course of time obtain more definite

results. In his conclusions the author states that the injection of immune and of normal human serum into the spinal canal during the acute febrile stage of poliomyelitis causes a distinct cellular reaction which is mostly polynuclear in type. The phagocytic action of these cells is beneficial in poliomyelitis. Such action is enhanced in immune serum by the presence of specific antibodies. It is preferable to use fresh serum, or serum which has been obtained under sterile precautions, passed through a Birkefeld filter and bottled without the addition of a preservative. The presence of a preservative and of hemoglobin in serum enhances its irritating effect, and gives rise to the more severe types of reaction. For purposes of treatment, it is important to diagnose the cases during the preparalytic stage of the disease by the typical group of early symptoms and the changes in the spinal fluid.

A Note on Sublingual Medication.—Cooper (*The Practitioner*, 1916, xcvii, 493) endorses the sublingual administration of hypodermic tablets in many cases where hypodermic medication seems inevitable, as in cases of severe vomiting, coma, esophageal obstruction, etc. The great advantage of the method is that it does not require any apparatus nor sterilization. He believes that this method has proved very effectual and is practically as prompt in action as when the remedies are used hypodermically.

The Treatment of Certain Diseases of the Skin by the Intravenous Injection of Foreign Protein.—Engman and McGoery (*Jour. Am. Med. Assn.*, 1916, lxvii, 1741) report the treatment of several forms of skin disease with the parenteral injection of foreign protein. The protein was obtained by using suspensions of typhoid organisms. The results were very favorable in such conditions as lupus, erythematosis, psoriasis, and several other types of dermatosis. Although the immediate results were satisfactory the treatment was often followed by relapse. They do not recommend this treatment for general use as yet but believe that its results are worthy of much further investigation.

The Diagnosis and Treatment of Hookworm Disease.—Billings and Hickley (*Jour. Am. Med. Assn.*, 1916, lxvii, 1908) say that thymol is the anthelmintic almost universally administered throughout the United States in the treatment of hookworm disease, and it was used exclusively in their hospital until one year ago, when oil of chenopodium was substituted. Since that time, owing to the encouraging results obtained, oil of chenopodium has been adopted as the regulation treatment to the exclusion of all others, the oil being of the variety known as the Baltimore oil. Compared with thymol, oil of chenopodium gives markedly better end-results, and its value is further enhanced by the facts that not only is it followed by fewer disagreeable after-effects but with its use no dietetic precautions need be exercised either before or during its administration. The routine course of treatments for adults is as follows: Preparatory treatment: At 7 A.M. magnesium sulphate, saturated solution 60 c.c. At 7 P.M., sodium sulphate, saturated solu-

tion 90 c.c. The next morning beginning at seven, oil of chenopodium is given in doses of fifteen drops (not minims), every two hours for three doses, followed by 18 c.c. of castor oil and 2 c.c. of chloroform two hours after the last dose of chenopodium. A second dose of 30 c.c. of castor oil is given a half-hour later. Chloroform seems to have a marked synergistic action, as giving chenopodium and omitting chloroform from the castor oil has been tried but with inferior results. The authors believe that the oil of chenopodium is absolutely safe when given as directed, with the additional value that it expels not only the hookworm' but also the roundworm, whipworm, tapeworm and the intestinal flukes.

The Treatment of Trichinosis with Thymol.—BOOTH, GOEHRING, and KOHN (*Jour. Am. Med. Assn.*, 1916, lxvii, 2000) state that the oral administration of thymol has been advocated for the treatment of trichinosis when the parasite is within the lumen of the intestine, but cases are seldom seen or diagnosed before lodgment of the parasites within the muscles and tissues of the body. It is futile to give thymol by mouth after the parasite has lodged itself in the muscle since the drug, after its absorption from the intestine, has its antiparasitic powers neutralized by the liver. Parenteral injections of thymol would exclude the conjugating action of the liver cells and a large percentage of the drug would be absorbed in the blood and would be carried to the muscles to attack the parasite *in situ*. They made use of a solution of 50 grains of thymol in 50 c.c. of sterile olive oil, which had been autoclaved for several minutes. The solution was then resterilized and the patient was given from 2 to 3 c.c. of this solution subcutaneously or intra- muscularly daily for seven days. The administration was then discon- tinued for several days and then again repeated. It was noticed that following the administration of thymol oil solution there was an increase in the percentage of the eosinophile leukocytes up to 30, 45 and as high as 55 per cent. This was no doubt due to the destruction of the parasite and the absorption of the parasite protein into the blood. There was no discomfort to the patient, except that a rash appeared on the palmar surfaces of the hands which cleared up when the administration of thymol was stopped.

Tonsillectomy during the Course of Rheumatic Fever.—NORRIS (*Jour. Lab. and Clin. Med.*, 1916, ii, 168) reviews the literature dealing with the close relationship between tonsillitis and acute rheumatic fever, and especially with the effects of tonsillectomy as a therapeutic pro- cedure. The general tendency has been to refrain from operating on tonsils acutely inflamed, especially when they are associated with acute joint involvement. The author deprecates this tendency and believes that there may be greater danger in deferring operation too late. If the tonsils are the source of infection, their continued presence increases the danger of secondary involvement of the heart. He believes that tonsillectomy is indicated as soon as the acute tonsillar inflammation subsides irrespective of the arthritic condition. He advises the use of salicylates in large doses to relieve the acute joint pains, before operating in order to increase the comfort of the patient.

PEDIATRICS

UNDER THE CHARGE OF

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Morbidity and Mortality of Pertussis and Measles, with Particular Reference to Age.—VEEDER (*Arch. Pediat.*, May, 1917, xxxiv, No. 5) presents a collection of statistics in charts and tables, from which he summarizes as follows: "A study of the morbidity and mortality of measles and pertussis brings out certain factors. Perhaps the most important of these is that, on an average, between 9000 and 10,000 deaths from each disease take place annually in the United States. While the death-rate as a whole, and for certain diseases as tuberculosis, diphtheria, diarrhea and enteritis under two years, and typhoid fever, shows a decrease in the registration area in the past fifteen years, that for measles and pertussis has remained practically the same. Surely no disease that causes one in every hundred deaths, or that rolls up an annual toll of between nine and ten thousand lives a year is insignificant or unimportant. A second point is the age distribution of the deaths in these two conditions. Nearly 80 per cent. of the pertussis and over half of the measles deaths occur in infants. The older the child the lower the case fatality rate. The widespread impression among the laity that it is a good thing to have these common infections of childhood early and get them over with is erroneous. The longer that they can be warded off, so much less the change of fatal or damaging complications. The mortality of the first year of life is greater than the combined mortality of the rest of childhood. A part of this—birth accidents—congenital malformations, etc., may be termed fixed and is irreducible, but far the larger part is preventable to a certain extent. Somewhere between 5 and 10 per cent. of the mortality which may be lessened is due to measles and pertussis."

Infective Theory of Acute Leukemia.—WARD (*British Jour. Children's Dis.*, January to March, 1917, xiv, Nos. 157–159) reviews 1457 cases of all varieties. He says, "The theory that leukemia is due to infection seems to derive most support from the acuter cases. Such cases are not infrequently admitted to fever hospitals, sometimes because of purpura and general symptoms, and sometimes owing to a definite membrane on the throat which closely resembles that of diphtheria." He admits that as yet no infective agent has been isolated. The cases on record of congenital leukemia give no clue of any source of infection in the mother or elsewhere. As regards leukemic mothers there is nothing in the records to show that their offspring tend to be leukemic, or that the mothers of leukemic children are leukemic. Of this series there are several cases in which this condition was present in two or more individuals who were members of the same household, but these are shown to be merely coincidences. He concludes that congenital acute leukemia is not infec-

tive, but that occasionally there is apparently infection of one person from another in older children and adults. He shows by charts that leukemia has a marked preference for the male sex; that chronic myelemia shows a majority of cases between 25 and 45; chronic lymphemia between 45 and 60; acute leukemia shows a decided preference for ages below 25. He recapitulates as follows: "The evidence of the facts here dealt with is almost entirely against the infective nature of leukemia, the established facts being: (1) That there is a congenital form of leukemia, which occurs in children whose parents are not leukemic. (2) That leukemic parents have never been known to transmit the disease to the newborn child. (3) That instances in which actual infection of one person by another might seem to have occurred are very few, although not necessarily devoid of significance. (4) That in having a marked preference for a particular sex and age leukemia differs from the infective class of diseases, and resembles the metabolic diseases and cancer.

Prodromal Symptoms of Infantile Paralysis.—WILSON (*Am. Jour. Dis. Children*, June, 1917). This paper is a study of 400 cases from the wards of the Willard-Parker Hospital, New York. Dr. Wilson takes up the prominent prodromal symptoms under the following headings: fever; gastro-intestinal symptoms; respiratory symptoms; nervous symptoms; urinary system; skin. *Fever:* Fever was the most common initial symptom, being noted in 334 of the 400 cases. Only 2 per cent had no history of fever. The fastigium was reached in twenty-four to forty-eight hours. The highest temperature reached was 106°; the average, 103°; the duration of febrile curve was from one to ten days; the average duration was four days; the temperature fell by crisis or lysis. *Gastro-intestinal Symptoms:* Vomiting was noted in 67 cases as the initial symptoms; as an early symptom in 132 cases. Constipation occurred in 156 cases. Diarrhea was not a common symptom, being present in 25 cases. Abdominal pain was an initial symptom in 21 cases; an early symptom in 25. It was usually severe and persisting several days, referred to the epigastrium and in two cases simulated appendicitis. *Respiratory Symptoms:* Throat. Sore throat was an initial symptoms in 21 cases; reddened in 27 cases; follicular tonsillitis in 14. On being admitted 100 cases showed injected fauces in 31; enlarged inflamed tonsils in 11; exudate in 4; mucopurulent discharge in 7. Epistaxis occurred in 2 cases initially. Coryza was noted in 17 cases. Conjunctivitis was noted in 9 cases. Cough was slight in 38 cases; in 2 it was severe. *Nervous Symptoms:* Drowsiness was early and characteristic in 288, or 72 per cent., varying from apathy to stupor in 47 cases. Irritability was present in 153 cases. This was associated with marked hyperesthesia in 97 cases. Tenderness and stiffness of the neck was an early and common symptom in 161 patients. Retraction of the neck and flexion of the lower extremities occurred in 40. Pain was seen in 130 cases, usually to neck, extremities, back and shoulders and chest. Tremor was present in 110 cases. Twitching was observed in 64 cases, sometimes choreiform in character. Twitching of the corner of the mouth sometimes preceded facial paralysis. Headache was noted in 78 cases; frontal or general headache was the first symptom in 12 cases. Convulsions was seen in 6 cases. Irritability in 3 cases. Delirium in 10.

Urinary System: 27 gave the history of urinary disturbance, usually a mild retention. Skin: Profuse sweating occurred in 45 cases. Rash: Red blotches in 2 cases; general erythema, 4 cases; macular, resembling measles, 8; urticaria, 4; pustular, 2; herpes, 7. Dr. Wilson notes in conclusion: "The prodromal period has been found to be the most important stage in the course of the disease, both as to early quarantine and treatment. A careful history while not diagnostic, is very suggestive particularly in an epidemic."

Occlusion of the Aqueduct of Silvius in Relation to Internal Hydrocephalus.—SCHLAPP and GERE (*Am. Jour. Pediat.*, June, 1917, xiii, No. 6). Eight cases are reported, all showing either complete occlusion of the aqueductus cerebri or obliteration of the fourth ventricle by severe pathological changes in the ependymal or subependymal tissue. "Those cases, also, developing acutely in previously healthy adults and older children, and which have shown microscopically the same pathologic changes, may have been brought about in the same manner, namely, through the stimulation by some chemical poisoning of a tissue which is embryologically defective. These cases, no doubt, differ etiologically from that large group following meningitis, the acute infectious diseases and those due to bacterial invasion of the brain substance and ependyma from extension of suppurative processes of the middle ear or of cells of the mastoid. A consideration of the life processes of the cell offers an explanation of the occurrence of many cases of congenital and acquired closure of the Sylvian aqueduct. Metabolism is nowhere more delicately expressed than in the highly complex chemical reactions of the cells of the central nervous system; and while knowledge of these reactions is still far from complete, it is, nevertheless, conceivable that any slight noxious influence may be sufficient seriously to disturb the latent forces of the glia cells, resulting in the dominating influence of one or the other of the processes residing in these cells. These life processes may be divided into the nutritive, the formative, and the functional activities. In the first, which involves an appropriation of nutritive substances from the blood, potential energy is stored up and is subsequently translated into formative or functional activity, as represented by cell division, on the one hand, or by functionation of the specialized cell, on the other. In cells which have become highly specialized, as the nerve cell, gland cell and muscle cell, the potential energy of the cell body is converted into the predominating activity, and the formative process is held in abeyance, and, so long as the normal relation between synthesis and catalysis is maintained, functional activity of the cell remains in a state of constancy. On the other hand, in those cells not highly specialized, as the ependymal, glia, and the connective-tissue cells, formative activity is easily awakened, and so it happens that in many cases of hydrocephalus, stimulation of these cells by some irritating substance results in an active proliferative process which involves not only the ependyma but the subependymal tissues of the aqueduct of Sylvius, as seen in the obliterative glioses (in these cases). The exact nature, source and means of access of such damaging stimuli are not always readily determined, and, barring the possible influence of syphilis and bacterial invasion of the meninges, ependyma and choroid plexuses, there remains to be studied more

closely the casual effects of circulating toxic by-products of fetal or maternal metabolism, and variation in function of the endocrine glands. Syphilis has not operated as a known etiological factor in this sequence, with the exception of Case 6, in which Spirocheta pallida have been found in the cerebral tissue. The Levaditi method has failed to show the presence of spirochetes in two other cases (2 and 7) which it was thought might be explained on the grounds of a luetic infection. The clinical records do not include reports of the Wassermann reaction of the blood or spinal fluids of the parents of these children."

OBSTETRICS

UNDER THE CHARGE OF

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Asphyxia Pallida from Placental Separation. — WELZ (*Am. Jour. Obst.*, November, 1916) reports the case of a primipara apparently near the end of pregnancy who had been taken with hemorrhage from the vagina, and uterine contractions had developed. On admission to hospital the patient was pale, with weak, rapid pulse, and no fetal sounds or movements could be recognized. The uterus was oval, relaxed and about the size of a nine months' pregnancy. On vaginal examination no placenta previa could be found. The membranes had not ruptured and there was considerable dilatation. Under ether the membranes were ruptured and bipolar version performed and the left leg of the child brought down. A fetus measuring 47 cm. in length was readily delivered in a condition of asphyxia pallida from which it was resuscitated by a lung motor. On examining the after-birth there were four distinct placentæ, the membranes traversed by numerous bloodvessels. The cord was attached to the center of the largest placenta, and the different placentæ were connected by the membranes which were unusually thick and vascular. The two larger placentæ were attached to the side of the uterus below the fundus, while the two smaller were in the lower uterine segment but were not placenta previa. The two lower had become detached causing hemorrhage.

Cholelithiasis Complicating Pregnancy.—FINKELSTONE (*Am. Jour. Obst.*, November, 1916) publishes the case of a multipara who when seen was pregnant between three and four months and who had an abortion. After this she was operated upon to repair lacerations, and following the operation had an attack of cholecystitis. It seemed to have resulted from the action of calomel given to the patient to move the bowels. From this she made a gradual recovery without operation, the roentgen ray showing adhesions around the gall-bladder. Sometime after this the patient became pregnant, refused operation, and had morphin to relieve pain. Consent was finally given to operation when

the gall-bladder was removed and found to contain 86 gall-stones of small size. The patient made a good recovery, the fistula healing in twenty-four days. Pregnancy was not interrupted and was then about seven months. The patient came into spontaneous labor later on and was delivered spontaneously of a full-term male child. Although there was extensive laceration it was repaired and she made a good recovery. Over a year afterward she reported with pain in the right epigastrium, apparently resulting from torn adhesions in the region where the gall-bladder had been. The use of a bismuth meal and roentgen ray was followed by temporary improvement after which the patient grew worse and suffered severe pain. Jaundice, vomiting of green material, and a gall-stone also occurred. There was a mass in the abdomen at the site of the gall-bladder. An operation was finally performed when the gall-bladder was found enlarged and chronic pancreatitis. The adhesions were separated and the gall-bladder removed, and the duo-denum drained. A small stone was found on examination imbedded in the wall of the gall-bladder. This patient for nearly a year had marked symptoms of cholecystitis without jaundice, gray stools, or fever. A drainage of the gall-bladder at the first operation did not disturb pregnancy and large doses of morphin given for pain apparently did not affect the child.

The Clinical Significance of Double Uterus.—Jones (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) reports the case of a patient brought to him in consultation in whom by examination it was found that a septum was present in the middle line of the vagina. On bimanual examination a separate cervix and uterus communicating with each could be plainly made out. The writer also reports the case of a mul-tipara who was seen in consultation ten days after her third confinement. The lochial discharge had been profuse and for three days offensive. The temperature was above 103° F. and the patient was evidently septic. The uterine cavity had been irrigated with a solution of iodin but the patient was not much better. Examination showed the uterus much larger than normal and its upper part irregular in outline. Under an anesthetic a double uterus was found with one cervix. One uterine cavity was normal for the stage of the puerperal period, in the other there was decomposing blood clots and the membrane of an early pregnancy. This mass was removed and the cavity irrigated when the patient went on to recovery. There had evidently been twin pregnancy, one on one side of the uterus going to term, the other a blighted ovum in the other cavity. Another case is reported in which a multipara had missed two periods and thought herself pregnant. Rather copious bleeding seemed to threaten abortion. When seen in consultation the conditions were such that anesthesia was necessary for examination. Two separate cervices were found and also two uterine bodies. In one of them was apparently a normal, growing ovum, and in the other some fungoid mucous membrane. This was removed by a curet and the patient went to term. In another case the patient had previously suffered from hemorrhage from the kidneys and was seen after she had been pregnant for two months and had two fetal sacks removed by ovum forceps at about the tenth week. In spite of this the abdomen increased steadily in size and pregnancy with living child was present. On

examination a double uterus was found. In this case there must have been a triple conception. In the next case the patient had been married more than four years, had interruption of pregnancy and a severe abdominal pain with enlargement on the left side of the uterus, and was thought to have ectopic gestation in the left tube. To make the diagnosis sure the abdomen was opened when a double uterus was found with pregnancy on one side. This went on naturally and the patient had a living child in a normal labor. A case came under the observation of the writer which shows how dangerous it is to use cutting instruments in the uterus unless an accurate diagnosis has been made. A primipara was delivered of a small child but the uterus remained large and the outlines of a second fetus could be made out. There seemed to be a thick septum between the two halves of the uterus or a very thick bag of water. Failing to rupture this with the finger the attending physician introduced a pair of long scissors into the uterine cavity and endeavored to cut the way into the fetal sack. Very severe hemorrhage came on which was checked but returned on the next day. The patient became infected and died on the fifth day from sepsis. At autopsy there was a double uterus and a fetus in the second uterine cavity and a ragged wound in the septum between the two bodies. Large branches of the uterine artery had been cut by the scissors. The tendency of this abnormality to interfere with labor is illustrated by the case of a multipara who previously had breech presentation with the birth of dead children. In a third confinement there were found two separate uteri and two separate cervices. Labor went on until the child descended when there was delay because the second uterus seemed to hinder expulsion and manual assistance was required. In the fourth labor this was repeated but pregnancy was in the anterior uterus and the posterior was drawn up above the level of the pelvic brim and occasioned no trouble. Involution was delayed but otherwise the patient made an uninterrupted recovery. A case is reported which illustrates the difficulty in diagnosis between a fibroid tumor in the uterus and pregnancy in a double uterus. The patient had three pregnancies and when four and a half months advanced was seen because she had intermittent hemorrhage. On examination the uterus was half-way to the umbilicus, somewhat flabby with an indefinite swelling on the left side of the uterine body. The outline of the upper border of the uterus showed a deep indentation and on the left side the tissues seemed more dense than on the right. The cervix was deeply split bilaterally and the endometrium thickened. The condition present suggested placenta previa or a sponge endometrium. It was thought that the mass on the left side of the uterus was a small fibroid although the possibility of double uterus was suggested. At seven and a half months the patient expelled a dead child. The placenta was removed by hand when it was easy to ascertain that the case was one of double uterus with pregnancy in the right body. That Cesarean section may be required in these cases is shown by a case who had two Cesarean sections before the one under consideration. At the last operation the operator had endeavored to sterilize the patient by removing the Fallopian tubes. The right tube was found and removed but the left could not be discovered, and pregnancy later supervened. At operation the anterior wall of the uterus was extremely thin at the

site of a former incision. When the uterus was opened the placenta was found in front and quickly delivered. The uterus was removed to sterilize the patient when the right half of a double uterus about the size of a goose egg was found behind a fold of the peritoneum extending from the posterior surface of the bladder to the rectum. A supravaginal hysterectomy was performed followed by recovery. The next patient had a very tender abdomen with a lump in the right side extending above the umbilicus. Examination was difficult because of pain, and the abdomen was opened under anesthesia for the removal of a tumor. The tumor was rising out of the pelvis with the bowel adhesive to it, and the great oventum attached to the tumor was darkly blood stained. The mass was a bicornuate uterus, the left side larger than the right. The left tube was filled with sterile fluid; adhesions were separated and a large clot removed from the peritoneal cavity. The left tube and ovary were removed and the abdomen closed; with the patient in the lithotomy position a large swelling could be demonstrated on the left side of the vagina. This was incised and retained blood washed out. It was then discovered that the patient had double uterus and vagina. Some months afterward the patient was readmitted complaining of pain. On this occasion, under anesthesia, vaginal examination showed that there was a septum between the two halves of the vagina and also a double uterus. The divided septum between the two vaginas was excised, followed by the complete recovery of the patient.

The Presence of Bacteria in the Vagina in the Latter Months of Pregnancy.—Permar (*Am. Jour. Obst.*, April, 1917) has studied 130 cases to ascertain what germs are present in the vagina in the latter months of pregnancy. Among these patients streptococci were never seen as such in direct smear, and by culture only 26 strains were recovered. Only 3 of these gave the carbohydrate reactions, and as animal inoculations were not carried out, the virulence of these strains was not known. In these investigations a variety of organisms were found. A relation apparently exists between the ability of various growths to flourish in an acid medium, and the presence of these organisms, notably the streptococci, the colon bacilli and other forms, in the vagina. The presence of streptococci giving the carbohydrate reaction is comparable to that recognized in other cavities of the body in which virulent or apparently virulent organisms are constantly present without causing active disease.

Bacteria in the Newborn Causing Septic Infection.—Hymanson and Hertz (*Am. Jour. Obst.*, April, 1917) have examined 42 newborn infants to determine the presence of bacteria in the cavities of the body. Of the 42 cases tabulated, the results were positive in 16, and negative in 26. In only 4 cases were the same organisms found in the body of the mother. In connection with the observation of others who studied this question, there is little evidence of infection of the infant's mouth on the first day after its birth, but on subsequent days infected bacteria grow and flourish and staphylococci predominates. It is not difficult to understand how such infection can occur in view of the presence of bacteria in the mother's birth canal and the frequent manipulation of the child's mouth in cleansing before and after nursing.

GYNECOLOGY

UNDER THE CHARGE OF

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Cystitis, with Special Reference to its Localization.—In a general review of our present knowledge of the bacteriology of cystitis, GERAGHTY (*Surg., Gynec. and Obst.,* 1917, xxiv, 655) says that while all the pyogenic bacteria are capable of producing inflammations of the bladder, and most of the known forms of bacteria have been isolated by investigators at one time or another, organisms of the colon group are the most frequent cause of cystitis, both acute and chronic. Bacteriological studies have further shown the old idea to be no longer tenable that an acid cystitis is usually due to the tubercle bacillus, for as a matter of fact, the urine in the vast majority of cases in simple cystitis is acid. The colon bacillus, the staphylococcus, different varieties of the streptococcus, the gonococcus, and many other organisms are usually associated with an acid cystitis, while organisms belonging to the proteus group usually produce an alkaline cystitis, with the well-known ammoniacal, ropy, mucoid condition of the urine. It is of interest to note, says the author, that there is a peculiar specificity displayed by different bacteria for different parts of the urinary tract. Thus, the primary focus of tuberculosis in the urinary tract is well known to be practically always in the kidney, vesical tuberculosis being secondary to the infection above, when it occurs. The gonococcus has a special predilection for the mucosa of the urethra; the only portion of the bladder commonly involved is the trigone, diffuse gonorrheal cystitis being extremely rare, while proven cases of gonorrheal infection of the kidney are rarer still. The typhoid bacillus, on the other hand, attacks principally the kidney, and usually produces a lesion of mild degree, resulting in nothing more than a bacilluria. The colon bacillus, staphylococcus, streptococcus, pyocyaneus, and some other organisms attack the kidney, bladder, and posterior urethra apparently with equal facility. With the possible exception of the tubercle bacillus, there is nothing characteristic in the lesions produced by these various bacteria, and it is impossible from the symptoms or pathology of a vesical lesion to determine the variety of invading organism, but so far as therapy is concerned, a knowledge of the organism concerned is of little real value, since no special drugs have as yet been shown to have any specificity of action for any special group of bacteria. With regard to treatment, Geraghty advises in acute cystitis the liberal employment of sedatives, in order to place the bladder at rest as much as possible. To aid in this, the amount of water ingested should be decreased to the absolute needs of the individual, so that the bladder will not be compelled to be constantly expelling the rapidly accumulating urine. To combat the increased acidity of the resulting concentrated urine, alkalies should be given to the point where the reaction becomes alkaline. Urotropin is useless, in the author's opinion, in these cases, since if the

urine is allowed to remain acid the fomaldehyde liberated only adds to the irritation, while if it is rendered alkaline, the urotropin is inert. Active treatment, such as instrumentation, irrigations, and instillations during the acute stage are usually more harmful than beneficial. If the symptoms do not rapidly subside, or the condition has become chronic, it is usually an indication that there is present some complication, either in the bladder itself or elsewhere in the urinary tract, whose discovery and elimination is of the utmost importance, since in most cases the successful treatment of a case of chronic cystitis will depend upon the ability of the physician to locate the intravesical or extravesical factor which is responsible for the continuance of the infection. In a certain number of cases, however, it must be admitted that the failure of the vesical infection to disappear spontaneously is not due to any extravesical factor. In most of these, the disease is not a diffuse cystitis, but is a localized affair, with normal mucous membrane lying between the infected areas, which latter may be single or multiple. Sometimes the lesion is a localized area of reddening and hyperemia, at others there is edema of the mucous membrane, and even the formation of bullæ and superficial ulcerations. When the lesion involves only the mucosa and to a slight extent the submucosa, simple irrigations with silver nitrate, or other silver salts, with overdistention of the bladder at each treatment, will generally suffice. If the involvement extends deeper into the bladder wall, however, such irrigations have but little effect. Here Geraghty fills the bladder with salt solution, and then through a ureteral catheter cut off square at the end, with no side eye, he injects directly against the infected area a 10 to 20 per cent. silver nitrate solution, which being instantly neutralized by the salt solution, does not irritate the remainder of the bladder mucosa. In some cases, there is found on cystoscopic examination a localized area in which the mucosa looks whiter than normal, with a puckered or scarred condition. Here one can feel reasonably sure that the condition involves the whole thickness of the bladder wall, and that no local applications will afford relief, but that extensive resection must be resorted to. These are the cases which have been especially studied by Hunner, whose work was reviewed in this department about two years ago.

Peritonitis following Acute Ovaritis of Anginal Origin.—According to WILDER (*Tr. Chicago Path. Soc.*, 1916, x, 46) hemogenic disease of the ovaries, arising by metastasis from disease of the tonsils or other distant foci, is probably more common than is usually supposed, and may account for many obscure cases of peritonitis. The occurrence of ovaritis as a sequel of general sepsis, measles, typhoid, cholera, and other infections has been observed, but the instances recorded are few, and the general tendency of gynecologists is to consider ovarian disease as a gonorrheal infection, ascending from the lower genital tract. It is significant, however, that of all reported cases of so-called primary peritonitis, a decided majority have occurred in females, this pre-dilection suggesting to the author the possibility that the sex organs play a significant role. Most of these cases occurred during the course of a tonsillar infection, and it seems more than probable that they were in reality metastatic infections from the throat. The following case in support of this theory is reported by Wilder: The patient was a child,

aged six years, who was seized with an attack of apparently ordinary tonsillitis. She complained of sore throat, and had a temperature of 103°, with large, edematous hyperemic tonsils, studded with white patches. The cervical and submaxillary lymph nodes were enlarged and tender. On the third day, when the throat condition was apparently improving, the child suddenly became acutely ill with symptoms of peritonitis. Immediate operation showed the peritoneum to be hyperemic and lusterless, with a small amount of thin pus in the pelvis. In spite of drainage the patient died in forty-eight hours, and autopsy showed an intense pelvic peritonitis, with much less involvement of the upper abdomen. There were no perforations, volvulus, or other demonstrable cause. The appendix was slightly hyperemic, but otherwise normal. The pelvic organs were all hyperemic, but the ovaries showed in addition some hemorrhages, and a few diplococci and short chain streptococci in the ovarian tissue. Cultures from the abdominal fluid at operation showed a pure growth of Gram-positive diplococci and short chain streptococci. Three quite similar cases from the literature are quoted by the author, who believes that these have all been cases of acute peritonitis, secondary to an ovarian metastasis from the throat infection.

Surgical Treatment of Benign Vesical Neoplasms.—The universally recognized treatment today for non-malignant intravesical growths— papillomata—is of course fulguration. As BEER (*Surg., Gynec. and Obst.*, 1917, xxiv, 646) points out, however, there are a few cases in which this method of treatment is not applicable. These fall under the following heads: (1) Patients that are intolerant to cystoscopy. With local anesthesia and morphin most of these can be overcome. (2) Patients that bleed furiously at every introduction of the cystoscope, so that no view can be obtained. (3) Patients whose tumors are so placed that they cannot be reached. (4) Patients suffering from papillomatosis of the bladder, either primary or following a surgical operation for papilloma, which operation has implanted many growths all over the bladder wall. For the small number of cases comprised in these groups, some form of cutting operation becomes necessary, but for the older method Beer substitutes an entirely new technic in order to safeguard the patient from the recurrences which almost invariably occur in the ordinary cystotomy performed for the removal of a papilloma. In Beer's method the intravesical operation is done entirely with the Paquelin (hooked point) cautery: the bladder is not filled with fluid before opening it; the incision in the bladder is gradually enlarged without any sponging or rough handling, and each tumor as it presents is burned to a crisp; every suspicious spot in the bladder is cauterized, and the edges of the bladder incision are similarly treated. Finally the whole operative field is soaked in alcohol to destroy any particles of viable growth that might have accidentally broken off during the manipulations. In order to get an adequate exposure the patient is placed in the Trendelenburg position and the bladder drawn out of the abdomen by its urachal end, this technic allowing the peritoneum to be stripped back without bruising the bladder or its contained growths.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Types of Lesions in Chronic Passive Congestion of the Liver.—
These lesions have been described by a variety of terms of which the
name nutmeg liver has been in most common use. It has, however,
been pointed out by not a few investigators that the character observed
in passive congestion of the liver giving it the nutmeg appearance, was
not uniformly the same. Moreover, there has been of late years a
considerable discussion concerning the question of the important
factors which brought about the tissue changes found in passive con-
gestion of different grades. To a great degree, the original contention
that the damage of the liver columns in the central portions of the lobule
was the result of unusual venous pressure, has now been dropped.
LAMBERT and ALLISON (*Johns Hopkins Hospital Bulletin*, 1916, xxvii,
350) have again reviewed the subject in a study of 112 cases of well
marked chronic passive congestion coming to autopsy. In the majority
of these cases the hepatic stasis was the result of a cardiac or vascular
lesion. The liver is commonly heavier than normal, the increased weight
being in part due to the excess blood present in the organ. A consider-
able difference in weight may be found in the same liver when weighed
immediately after removal and when weighed again sometime later.
The appearance of the cut liver varied with the duration of the circu-
latory disturbance, and, although some common features could be
recognized in all specimens, yet a close analysis readily distinguished
types permitting of a classification. An interesting point made by these
authors is that under the conditions of these hepatic lesions the liver
demonstrates a poor ability for regeneration. And, furthermore,
regeneration was not most active in the specimens from young indi-
viduals but was rather associated with the chronic lesions in middle
age or elderly individuals. This is probably due to the fact that
examples of chronic congestion are found more often in old people;
whereas in the young the acute stage of the same process is found prior
to the period of regeneration. These authors have found five distinct
types of lesion in passive congestion of the liver. These types are to
some degree at least, merely stages of one and the same process; in
fact it would appear that any one of the type lesions may progress to the
next grade in severity by increasing either the duration or the severity
of the blood stasis. These five types are determined by microscopic

analyses and are dependent upon the grade of dilatation of the liver sinuses and the degree of atrophy or necrosis of the liver cells. The types are as follows: (1) Capillary dilatation with atrophy of central cells, found in moderate circulatory disturbances of various kinds; (2) central degeneration with or without congestion, a stage of degeneration slightly more advanced than the preceding; (3) central fat accumulation with hyperemia or necrosis, a peculiar type usually found in the young in acute rheumatic fever; (4) central necrosis usually associated with hemorrhage, the advanced nutmeg lesion described by Mallory; (5) collapse fibrosis or cardiac cirrhosis. This last condition is more apparent than real, there being little if any increase in the amount of connective tissue originally possessed by the liver. The important factors which lead to the various changes in the liver substance are blood stasis, tissue asphyxia, interstitial hemorrhage and autolysis. The actual effect of the blood-pressure upon surrounding tissues appears to be slight.

The Comparative Resistance of Bacteria and Human Tissue Cells to Certain Common Antiseptics.—LAMBERT *(Jour. Exper. Med.,* 1916, xxiv, 683) discusses some interesting experiments performed by him to determine the comparative effects of antiseptics on bacteria and tissue cells of humans. Tissue of lymph glands removed at operation or autopsy was grown in a plasma medium with Staphylococcus aureus. He used this organism because it is moderately but not highly resistant to the ordinary antiseptics. The antiseptics used were mercurials, cyanides, iodin, phenol, tricresol, argyrol, alcohol, hypochlorites and a few others. The technic was as follows, thin layers of tissue were placed in a fluid culture of staphylococcus for several minutes. They were then transferred to the disinfectant solution for one hour, then washed in isotonic salt and placed in the plasma medium. Controls of infected, non-treated tissue and non-infected tissue were made. Most of the chemicals were found to be more harmful to the tissue cells than to the bacteria; in fact, the one marked instance of the opposite result was in the test with dilute iodin ($\frac{1}{2500}$ to $\frac{1}{1500}$). It was found with this chemical, however, that application of it to fibrin caused a dissolution of the fibrin even though it did not injure the tissue cells. Alcohol was potent only in 50 per cent. solutions and had an inhibitory effect on the growth of cells in this strength, although in weaker dilutions it stimulated rather than inhibited the growth of the tissue used. The author concludes that of the many antiseptics tried, iodin is more clearly an ideal antiseptic than any of the others.

A Study of Physiological Activity of Adenomata of the Thyroid Gland, in Relation to Iodin Content as Evidenced by Feeding Experiments on Tadpoles.—Previous experimenters have shown that the feeding of dried thyroid to tadpoles causes an early differentiation of structures in proportion to the quantity fed or the percentage of the iodin content. GRAHAM *(Jour. Exper. Med.,* 1916, xxiv, 345) used this method to determine the physiological activity of adenomatous tissue of the thyroid as compared with normal thyroid substance. For the feeding experiments, human thyroid and its adenomata were used. The material was fed to tadpoles and observations were made upon their

growth from day to day. Numerous protocols are given for some of the experiments. The author found that the so-called adenomata of the thyroid possess characters which influence the development of tadpoles in a manner quite similar to that of the normal thyroid. The action appears to be dependent upon the iodin content. The results of these feeding experiments were not so simple to interpret as might appear at first sight. Discrepancies as to the time of death, appearance of forelegs, emaciation and rate of growth were not always parallel to the iodin content. Some of these discrepancies, the author believes, may be explained by accident of feeding or slight differences of age, size and susceptibility to the materials fed. The action of the thyroid depends not upon a specific stimulus to differentiation but upon a stimulation to metabolism in general, in proportion to the iodin consumed. High iodin content produces rapid emaciation, at the time resulting in differentiation even in tadpoles dying in eight to twelve days. Low iodin content results in differentiation at an earlier period than the controls. Tadpoles fed on thyroid with practically no iodin grow better than controls, the thyroid serving simply as a food. In the experiments undertaken the author points out that as the active principle of the thyroid was demonstrated in the adenomata these tumorous masses have a functional capacity.

Technic of Cultivating Human Tissues in Vitro.—Various attempts have been made to cultivate human connective tissue *in vitro* in a culture medium of a pure human plasma, but practically all have been failures, owing to the early rapid liquefaction of the fibrin. The modifications of this human plasma made by Losee and Ebeling were unsuccessful. However, by diluting the plasma with Ringer's solution, as recommended by Carrel, they were able to propagate human connective tissue cells through several subcultures, in one case as long as sixty days, by making the transfers every twenty-four to forty-eight hours. LAMBERT (*Jour. Exper. Med.*, 1916, xxiv, 367) in the cultivation of the tissues of lower animals noted that the plasma of pigeons and fowls never liquefied. He therefore prepared a mixture of a small amount of chick plasma with a considerable quantity of human serum, into which he put various human tissues obtained at operation. No liquefaction occurred and active progressive growth, with numerous mitotic figures, was seen in the majority of preparations in which soft friable tissue was used. After careful study the author found that the optimum medium consisted of 1 part fowl plasma to 4 parts human serum; growth in pure fowl plasma was possible though neither so active nor prolonged as in a mixture. The author states that transfers did not have to be made oftener than every five days, and that propagation through subcultures might be carried on for several months and *in vitro* indefinitely. In addition to experiments on culture medium the author studied the length of time that tissues may be preserved after their removal from the body. They were placed in salt solution in a Petri dish and put in an ordinary wooden ice-box whose temperature ranged from 10° to 15° C. The results of these studies showed that human connective-tissue cells and the cells of certain benign tumors remain alive in an ice-box from six to eight days, ten days probably representing the limit of survival. The optimum temperature for such preservation

was not determined. Tissues obtained at operation gave the best results, but autopsy material removed one to four hours after death sometimes showed active growth. The author, in the performance of these various experiments, also made note of the fact that the presence of normally existing iso-antibodies (agglutinins and hemolysins) in human serum was without influence on the growth of human tissues *in vitro*. In other words, human tissues are no more sensitive to variations in the culture medium than are those of the lower animals. Hence autogenous serum has no advantage in tissue culture over homologous serum.

The Classification of Streptococci.—There is no subject in the field of bacteriology of wider interest which although receiving much attention and study for practical application has still remained in a chaotic state from the stand-point of classification, than the streptococci. Many attempts have been made to classify the streptococci and not a few of them have served a useful purpose inasfar as they could be applied. Broadly, however, certain modes of classification have, up to the present, not lent themselves as being practical. This is particularly true of the immune reactions. The mode of classification has, therefore, again reverted to the adoption of a practical method based upon cultural procedure. Such a classification has been put together by HOLMAN (*Jour. Med. Res.*, 1915, xxxiv, 377). In this classification he has introduced no new media or reactions but by analyzing, in the study of a great number of streoptococci, the value of many cultures and reagents suggested by others, he has eliminated those of no practical importance and retained others having a differential value. Holman points out that for any classification of bacteria based upon cultural methods a standard procedure for the making of the media must be adopted. For the group of streptococci where special media other than those employed for the coli-typhi group are necessary, there has, up to the present, been no uniformity of technic. Holman describes clearly his procedure for the isolation, plating and differential cultivation of the streptococci. This group of microörganisms presents some difficulties not so prominent with other bacteria. One of these, which appears to have been overlooked by others, is that of obtaining pure cultures. Holman has found that when the pure strain has been obtained the cultural characters upon the differential media used are quite permanent. The streptococci which he has under discussion are non-capsulated forms. He divides the streptococci into two groups by means of blood agar. The further differentiation is accomplished by means of serum broths containing lactose, mannit, and salicin respectively. Thus under each of the two main groups, the hemolyzing and non-hemolyzing streptococci, there are developed eight distinct subgroups depending upon the fermentation or non-fermentation of the given carbohydrates. Five of the hemolytic varieties are known by definite names: S. infrequens, S. pyogenes, S. anginosus, S. equi, S. subacidus. Five distinctive names have also been applied to varieties of the non-hemolytic streptococci: S. fecalis, S. mitis, S. salivarius, S. equinus, S. ignavus. The author has tested out over 1100 strains by means of this classification and he has also applied the method of classification to 2400 streptococci isolated by others. The practical application of this means

of classification has shown that the organisms found in distinct habitats remain true to form and it is often possible to suggest the source of an infection by the cultural characteristics determined by this technic. The work marks a distinct advance in our knowledge of streptococci. Those who are more particularly interested in this subject must consult the original article.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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An Epidemic Resulting from the Contamination of Ice-cream by a Typhoid Carrier.—CUMMING (*Jour. Am. Med. Assn.*, April 21, 1917, lxviii, No. 16, 1163) reports the following outbreak: Twenty-nine persons attended a country school picnic at Helm, California, May 13, 1916. That evening many of those in attendance were taken with nausea, vomiting, and diarrhea. These symptoms were of about two days' duration, and with two exceptions all those thus affected developed typhoid fever in about eight days. Twenty-three persons in all came down with the disease, 3 of whom died. It was found that all of those who were made ill had eaten chocolate ice-cream. All those who partook of this food developed typhoid fever with two exceptions, namely, Mrs. Y., who made the chocolate ice-cream, and her daughter, both of whom, however, suffered from nausea, vomiting, and diarrhea. It was found that Mrs. Y. was a typhoid carrier who had had the disease seventeen years before, and had been responsible for at least four other cases of typhoid fever in persons living in her household during the seventeen years. Her daughter escaped the disease, having had antityphoid vaccine two years previously. The outbreak is further interesting for the reason that Mrs. Y.'s blood agglutinated typhoid cultures only in dilution of 1 to 50 and then incompletely. The California State Board of Health makes an effort to keep in touch with all typhoid carriers, not only for the purpose of directing their daily pursuits along lines which will not endanger the public health, but also for the purpose of making investigations of the carrier problem. Typhoid carriers are not isolated but are required to sign an agreement to take no part in the preparation or handling of food which may be consumed by persons outside of their immediate family, nor to participate in the management of a boarding-house, restaurant, food store, or any other occupation involving the prepara-

tion or handling of food. The carriers also agree to take precautions with reference to the disposal of excreta, and to notify the local health officer in case of change of residence, and to comply with other requirements. This contract is renewed every six months. The author concludes that the typhoid history of Mrs. Y. demonstrates the inefficacy, from the standpoint of community health, of treating a case of typhoid without seeking the source of the infection. It is seventeen years since she herself had typhoid; there are many isolated cases of the disease reported among those with whom she came in contact; finally, this epidemic, traced indubitably to her, occurred. Had the first case, years ago, for which she may have been responsible, been traced to its source, the subsequent cases, the economic loss to the community, and the three deaths could have been avoided.

Detection of Hydrocyanic Acid Gas.—GRUBBS (*Public Health Reports*, April 20, 1917, p. 565) states that instructions issued to the officers of the Public Health Service on the subject of hydrocyanic gas fumigation of vessels directed that "Before declaring it safe to enter holds, a captive animal (guinea-pig, rat, cat, etc.) shall be lowered and exposed to the aërial content of such compartments, and the effect produced, if any, shall be a guide in estimating the amount of gas present." In trying to determine just what dilution of hydrocyanic acid gas should be considered dangerous to man, volunteers have breathed gas from one-half and from three-fourths ounce sodium cyanide per 1000 cubic feet for two minutes and one and one-half minutes respectively, without feeling any effect, but this has at other times caused dizziness. Grubbs believes that where work must be done and a climb is required to reach the open air a mixture of 0.024 per cent. hydrocyanic acid gas (one-half ounce sodium cyanide per 1000 cubic feet) should be considered the limit of safety. With this limitation in mind the susceptibility of small animals usually available for the purpose of testing holds was studied, and the following conclusions reached: Sparrows or other small birds are the most delicate live indicators for hydrocyanic acid gas, but are not recommended for routine work; mice or tame rats are almost as susceptible as sparrows and are probably the best test animals available; cats are sufficiently susceptible and with care the same animal may be used several times; guinea-pigs are quite resistant to the effects of the gas and should never be used where rats are available; if guinea-pigs be the only test animals obtainable, exposure should be prolonged and other allowances made for these animals' increased resistance to the gas.

Weil's Disease or Infectious Jaundice.—NOGUCHI (*Jour. Exper. Med.*, May 1, 1917, xxv, No. 5) atates that infectious jaundice has been known for a long time to occur among troops in barracks, among sewer workers, miners, and rice planters, and its clinical entity has been recognized by Larrey, Ozanam (1849), Monneret (1859), Laverau (1865), Lancerau (1882), Landouzy (1882), Mathieu (1886), and Weil (1886). Weil described 4 cases with typical symptoms, and the disease is very often called by his name. Weil's disease is characterized by sudden onset of malaise, often intense muscular pains, high

fever for several days, followed by jaundice and the appearance of bile pigments, albumin, and casts in the urine; in severe cases epistaxis, subcutaneous hemorrhages and lymphadenitis are observed. A disease supposed to be identical with Weil's disease of Europe is prevalent in Japan, and in 1914 Inada and Ido succeeded in transmitting to guinea-pigs the typical experimental disease, accompanied by jaundice, hemorrhages, albuminuria, etc., by inoculating them with blood of patients suffering from the Japanese form of infectious jaundice. In the blood and various organs of the animals they discovered a new spirochete, which they also found in the human specimens. Spirocheta icterohemorrhagiæ, as it was designated by Inada and his associates, has since been proved beyond doubt to be the causative agent of the disease in question. A year and a half later, Uhlenhuth and Fromme, and also Hubener and Reiter, showed that the Weil's disease prevalent among the German soldiers during the present war could also be transmitted to guinea-pigs by injecting them with the blood of patients. It was not until 1916, however, that Hubener and Reiter announced the finding of a spirochete in the experimental material (liver, blood, kidney, etc.), which they called Spirocheta nodosa. Following the publication in America of the article by Inada and his collaborators, Stokes and Ryle succeeded in transmitting the disease to guinea-pigs by inoculating them with the blood of British soldiers in Flanders who had Weil's disease, confirming at the same time the presence of a spirochete closely resembling the Spirocheta icterohemorrhagiæ of the Japanese workers. Stokes, Ryle and Tytler left the question of the identity of the two strains (the Belgian and the Japanese) open for future discussion. In the meanwhile, Martin and Pettit, Costa and Trosisier, Garnier and Reilly, Renaux, Merklen and Lioust, Ameuille, Salomon and Neveu, and others, working among the French soldiers on the western front, reported similar clinical and experimental findings. They also considered the spirochete isolated from the French specimens to be closely related to the Japanese strain. On the Italian front numerous cases of jaundice have been observed, and Monti has demonstrated the spirochete in the experimental material. According to MacKenzie, there were at one time a considerable number of cases of infectious jaundice among the Canadian soldiers stationed at Salonica. It is of interest to note that while the mortality among the Japanese is as high as 38 per cent., that of the European soldiers did not exceed 2 to 3 per cent. It seems reasonable to assume that the Japanese strain has already acquired a marked increase in virulence for human subjects, owing probably to a more frequent passage from man to man. Such transmission is more frequent in Japan, for example, among the rice planters and miners with imperfectly protected feet, than in Europe, where exposure to the infection was brought about only through the unsanitary conditions of war. The entrance of this spirochete into the human body seems to be of comparatively recent occurrence. The discovery of the spirochete in apparently healthy wild rats caught near the infected districts seems to support the theory that the disease was originally epizoötic among certain rodents, particularly wild rats, and after a long sojourn in this species of hosts its virulence for these animals has been reduced to such an extent as to cause the latter no

inconvenience, or, at least, a state of tolerance for the spirochete has developed. In America, especially in the United States, there have been few epidemic or endemic cases of infectious jaundice reported from various quarters of the continent (Toronto, Middle Western and Southern United States) and from Cuba, but it was not known whether or not these cases corresponded with those found in Europe and Asia. The discovery of the specific pathogenic agent now enables us to answer this question experimentally. The author collected a large number of wild rats and removed their kidneys for the purpose of ascertaining whether or not the organs contained the spirochete which causes the typical experimental lesions characteristic of the organism of infectious jaundice. By inoculating the emulsion into guinea-pigs, he has been able to produce a typical icterohemorrhagic spirochetosis altogether identical with the findings in the guinea-pigs which died of the injections of the Japanese and Belgian strains of Spirocheta interohemorrhagiæ. The strain of spirochete isolated produced death in from nine to twelve days, attended by marked jaundice, cholemia, choluria, and extensive hemorrhages in various viscera, The author concludes that wild rats captured in this country carry in their kidneys a spirochete which possesses the morphological and pathogenic properties characteristic of Spirocheta icterohemorrhagiæ discovered by Inada in the Japanese form of infectious jaundice. Cultures of the American, Belgian, and Japanese strains of the spirochete were obtained by a special technic, the first two strains having been cultivated artificially for the first time. Animals actively immunized against the Japanese strain resist inoculation, not only of the same strain, but also of the Belgian and American strains. The Belgian strain produces immunity equally effective against all three strains. Experiments to ascertain whether the immunity afforded by the American strain also protects against the Japanese and Belgian strains are in progress. These findings warrant the conclusion that the spirochetes designated as the Japanese, Belgian, and American are probably identical. On account of its distinctive features, a new genus, Leptospira, has been suggested as the designation of this organism.

Some Factors Alleged to Influence the Duration and Severity of Vaccinia.—FORCE and STEVENS (*Jour. Am. Med. Assn.*, April 28, 1917, lxviii, No. 17, 1247) find that in the course of normal vaccinia, the maximum development occurs on the tenth day and scab separation takes place on the twentieth day after vaccination. Dyer ("The Way to Vaccinate," *Am. Jour. Trop. Dis. and Prev. Med.*, 1913, i, 425) paints the vesicles with tincture of iodin, clips the top with sterile scissors, and cauterizes the base with a 6 per cent. solution of silver nitrate. Unna ("Nawssende Ekzeme," *Berl. klin. Wehnschr.*, 1915, lii, 281) applies a mixture of 8 parts of zinc oxide ointment with 1 part each of calcium carbonate and sulphur lotum. Schamberg and Kolmer ("Treatment of the Vaccination Site with Picric Acid Solution," *Lancet*, London, 1911, ii, 1397) paint the vesicle at the end of forty-eight hours with a 5 per cent. alcoholic solution of picric acid. Force and Stevens tested these three methods and found that they did not possess any advantage so far as decreasing the redness and shortening the course of the vaccinia is concerned.

Provocative and Prophylactic Vaccination in the Vaginitis of Children.—A. F. Hess (*Am. Jour. Dis. Child.*, November, 1916, xii, 466–476) states that postmortem examinations show that in the subacute and chronic cases of vaginitis in infants, the cervix is most frequently involved and that the vagina generally shows no signs of inflammation. Cervicitis would therefore seem to be a more correct term, in this connection, than vaginitis. When numerous pus cells without bacteria are found in smears made from the cervix, an inflammation may be assumed to be present, and in the overwhelming majority of instances the inciting factor will be found to be the gonococcus. Other microörganisms may, however, be the cause of the inflammatory process, for example a streptococcus. It should be borne in mind that smears taken from newborn infants very frequently show pus cells, probably due to the invasion of the vagina by saprophytic bacteria, and that, in the newborn, they should not be considered pathological or as evidence of gonococcal inflammation. Gonorrheal vaginitis, or cervicitis, should not be regarded as a disease encountered especially in institutions, as it may be found in a considerable proportion of infants living in the crowded tenements in the city. In child caring institutions, the greatest obstacle to limiting and controlling the spread of this disease is the difficulty of recognizing latent cases. By means of provocative inoculations of gonococcus vaccine, we have found it possible to convert the concealed carrier into an open case, and in this way to discover many cases which had eluded detection. Vaccinations have also some prophylactic value, and may either confer protection or render subsequent infection of a mild character, so that it assumes a bacteriological rather than a clinical type. There is not only a natural susceptibility to this infection and an acquired susceptibility, as occurs in the course of scarlet fever, but a natural immunity, which may be sufficient to protect infants who come in contact with infected patients.

The Virulence of Diphtheria Bacilli from Diphtheria Patients and Diphtheria-carriers.—Weaver (*Jour. Infect. Dis.*, February, 1917, xx, No. 2) states that diphtheria bacilli from patients with diphtheria and from carriers who have been in contact with such patients are practically always virulent. The bacilli in such cases usually remain virulent up to the time of disappearance, even though a long time has elapsed. Carriers should be kept in isolation until the bacilli have been gotten rid of, or until the strains cultivated have been proved to be non-virulent. Cultures from the nose as well as from the throat should be made in all suspected cases.

ORIGINAL ARTICLES

A CASE OF ADAMANTINOMA SHOWING EPITHELIAL PEARLS.

By Stuart Graves, M.D.,

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(From the Pathological Laboratory of the Medical Department of the University of Louisville and of the Louisville City Hospital.)

Tumors arising from embryonic structures of the teeth are comparatively rare. The majority of such neoplasms are reported as "odontomata." According to Mallory,[1] three types of tumors of the jaw are recognized as arising from embryonic remains of the enamel organ. These are:

1. The follicular cyst, which is the simplest. It consists of a cyst lined with pavement epithelium. The inner wall of the cyst often bears a single, rarely several to many teeth.

2. The adamantinoma, growing as branching masses of epithelial cells, of which those adjoining the stroma correspond to adamantoblasts while the others form the enamel pulp. Cysts often form, owing to distention and coalescence of the vacuoles lying between the cells corresponding to those in the enamel pulp. Other cysts, which may be more numerous and larger, often occur in the connective tissue of the stroma as the result of focal collections of fluid. Bloodvessels will always be found running through this second form of cyst. Rarely the cells corresponding to those in the enamel pulp assume a concentric arrangement or may even form definite epithelial pearls. This result is not surprising, considering the origin of the enamel organ. The adamantinoma grows expansively only and

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[1] Principles of Pathological Histology, second edition, p. 285.

does not produce metastases.   Owing to its location and the size it
sometimes reaches it may cause clinically much local disturbance.

3. The odontoma, which is produced by the conversion of fibro-
blasts adjoining the adamantoblasts into odontoblasts as a result
of the action of the adamantoblasts upon the fibroblasts.   When this
happens separate teeth or fused masses of them may be produced
by the differentiation of the odontoblasts with the adamantoblasts.
Cementum may sometimes be formed.   Occasionally the adaman-
tinoma produces typical enamel.

Fig. 1.—Adamantinoma.   Cysts forming between pulp cells.   Multiplied 150.

Adamantoblastoma, then, is a generic term like fibroblastoma,
and covers the adamantinoma, developing from epiblastic cells which
normally differentiate into adult enamel, and the odontoma, includ-
ing not only the tumor structures of the adamantinoma, but also
those structures arising from mesoblastic odontoblasts which nor-
mally differentiate into dental pulp, dentine, and cement.   The
structures of the adamantinoma are included in the odontoma
because the structures of the latter are stimulated to growth by the
action of the adamantoblasts upon the mesoblastic stroma, just as
proliferative activity on the part of fibroblasts is incited by other
tumor cells.   The odontoma is a more highly differentiated type of
adamantoblastoma just as a dermoid cyst is a more highly differen-
tiated form of embryoblastoma than is a rapidly growing embryoma,

more commonly called a round or spindle-cell sarcoma or a carcinoma.

The adamantoblasts normally begin as an invagination of the oral epithelium and develop into the enamel organ covering the mesenchymal dental papilla.   The enamel organ consists of an outer layer of enamel cells lying next to the surrounding gum and an inner layer of enamel cells lying next to the dental papilla.   Between the two layers is the enamel pulp, consisting of epithelial cells corresponding to the prickle cells of the epidermis.   "At first these internal cells are in close contact, like those of ordinary epithelium; but later, through vacuolization and accumulation of gelatinous, intercellular substance, they constitute a protoplasmic reticulum which resembles mesenchyma, and is known as the enamel pulp."[2] An excessive accumulation of this secretion, with abnormal coalescence and distention of the spaces, gives rise in tumors to cysts filled
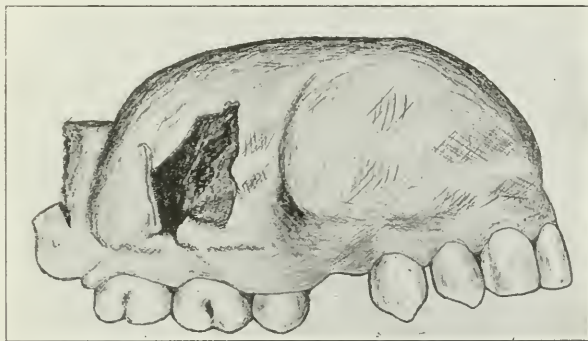
Fig. 2.—Adamantinoma reproduced with pen and ink from Kaiserling preservation of lateral half of specimen and from written description.   (McCrocklin.)

with gelatinous, sticky, semifluid material.   Larger cysts are also formed in the stroma of such tumors by the accumulation of fluid, and are surrounded with cylindrical cells whose nuclei are away from the stroma, and hence from the cysts.   These two kinds of cysts are characteristic of the cystic adamantoblastomas.   In the normal embryonic enamel pulp no vessels or nerves are found, but in the stroma of neoplastic growths arising from remains of the enamel organ, vessels do occur as they do in the stroma of all tumors.   The larger cysts form about these vessels.

In the process of invagination and development of the enamel organ the inner enamel cells (ameloblasts) elongate and become the enamel-producing cells (adamantoblasts).   According to Lewis and Stohr[3] "the ameloblasts produce enamel along their basal surfaces, which are toward the dental papilla; but they become so trans-

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[2] Lewis and Stohr: A Text-book of Histology, second edition, p. 102.
[3] Loc. cit.

formed that their basal surfaces appear like free surfaces and the
entire cells seem inverted. In columnar epithelial cells the nuclei
are generally basal and the secretion gathers near the free surface,
but in the ameloblasts these conditions are reversed. The nuclei
are toward the enamel pulp and the latter forms a dense layer over
the ameloblasts,'' while what were the basal ends of the cells before
invagination, which now lie next to the dental papilla, appear free
and without nuclei. In the microscopic picture of adamantoblas-
toma most of the cysts are in the stroma, as a rule, and are lined with
the apparent free ends of the cylindrical epithelium whose nuclei
are in the opposite ends away from the cysts. In other words, the
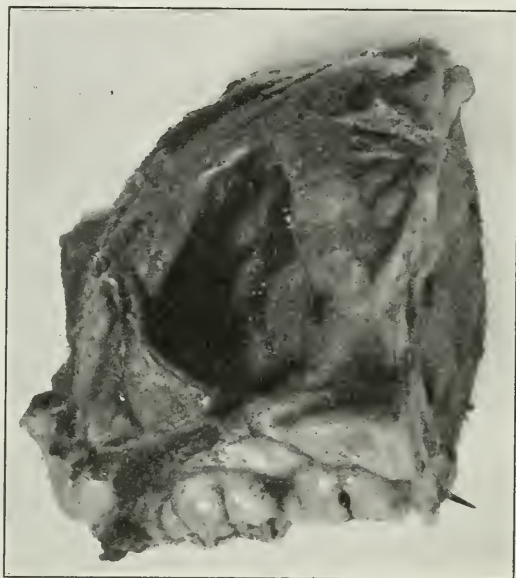
FIG. 3.—Adamantinoma, from photograph of Kaiserling. Preservation of lateral
half of specimen.

ends which were basal before invagination and contained the nuclei
are now free and adjacent to the cysts in the stroma. This is another
characteristic picture of adamantoblastoma.

In connection with the case herein reported it is interesting to
note that it occurred in a negro child. Miller,[4] in presenting
clinically a case of unilateral odontoma of the superior maxilla in a
two-year-old colored child, diagnosed with the aid of skiagrams
which showed numerous widely scattered teeth, says: "Slowly
growing unilateral jaw tumors are not infrequent in colored people
and often attain huge size. These are commonly odontomata or

[4] Philadelphia Acad. Surg., 1914, xvi, 35.

adamantine in character." Westmoreland,[5] in presenting a tumor which he called a "follicular odontoma" in Bland-Sutton's classification, made the observation that these tumors seemed to be disappearing, he not having seen a case for years, although he had operated on 5 cases and his father on 38, all save one in negroes.

This report is submitted because it is that of an adamantinoma developing purely from adamantoblasts, shows epithelial pearls, and occurred in a sixteen-year-old negro boy. The specimen was removed by Dr. H. H. Grant from the superior maxilla on March 1, 1916, in the Louisville City Hospital and was sent to the laboratory with a clinical diagnosis of osteosarcoma. The tumor had been first
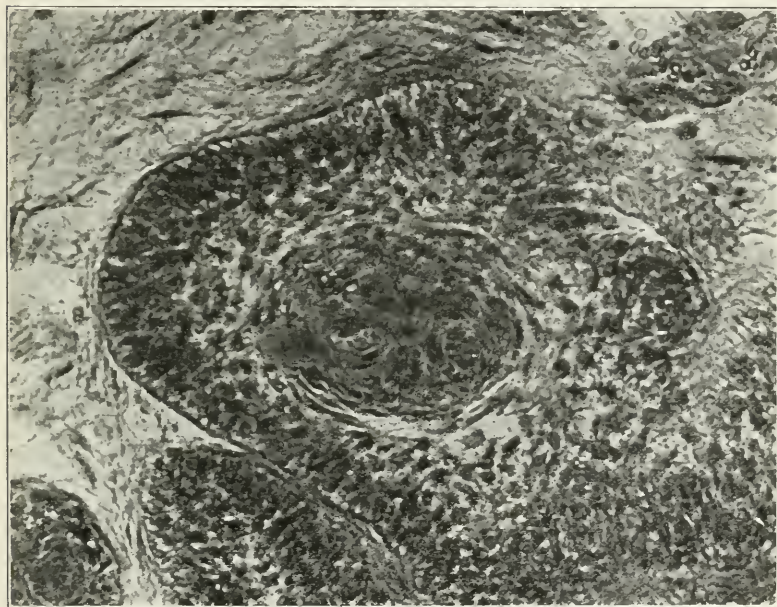
Fig. 4.—Adamantinoma, showing epithelial pearls.   Multiplied 400.

noticed about one year before as a swelling of the gum, had grown gradually and been painless. The gross description of the specimen is as follows:

GROSS DESCRIPTION. Specimen consists of a portion of right superior maxilla with tumor. Three incisors, one canine, two molars, and adjacent bicuspid are present in their normal positions. Shaft of bone is severed transversely 1 cm. outside of lateral molar. Its superior surface is smooth and covered with muscle. Medial end is 2 cm. at left of cleft, between middle incisors. Anterosuperior surface bears a rounded mass covering practically all the surface.

Mass presents a cavity extending from upper to lower margins of specimen, 25 mm. wide and 15 mm. deep anteroposteriorly. This cavity is covered in front with a firm, cartilaginous shell, 1 to 3 mm. thick, and opens anteriorly in lower portion through an orifice 15 x 25 mm. Inner surface of cavity is smooth and does not present any teeth. Greater portion of remainder is smooth, moderately firm, and covered with a fibrous capsule bearing tags of muscle in upper portion, and presents a transverse, ragged crevice, apparently artificial. Tumor mass extends around underneath gum between canine and lateral bicuspid. In this space it is smooth, pale, and moderately firm. On sagittal section, through middle of mass, cut surface presents inferiorly, hard, cancellous bone 7 mm. thick, which extends upward about two-thirds of circumference of posterior surface. Anterosuperiorly tumor is bounded by a very thin, pale, white shell. Between these limits the tissue varies from white and pale gray, firm tissue to soft, pink and pale creamy brown tissue. Scattered in cut surface are small, irregular, pale spots cartilaginous to bony in consistency. On sagittal section through bicuspid there is opened anteriorly a smooth-walled cyst, unilocular, bounded by a thin, pale membrane, and containing pale brown fluid material distinctly gelatinous. It sticks to fingers like secretion from thyroid. This cyst is 15 mm. in greatest diameter and its bottom is 12 mm. above root of bicuspid. A smaller, similar cyst lies peripherally at superoposterior border of the specimen. Another sagittal section medial to first shows cut surface circumscribed as others, but solid and varying from pale gray to straw color and from bony hardness to soft. From surface of this is given off considerably more stringy, gelatinous material. After fixation numerous small holes are seen in cut surface. Sagittal section of one tooth in normal position shows root imbedded in maxilla at base of tumor mass. Sections of one-half of the specimen do not reveal any signs of teeth within the tumor.

MICROSCOPIC DESCRIPTION. Ten sections through different parts of the tumor show more or less similar structures; small to fairly large, irregular, sharply outlined, branching masses of compact cells. The grouping of the tumor cells suggests the arrangement of the compact epithelial cells in a hair matrix carcinoma. These are supported by a fibroblastic stroma in which is seen an occasional small vessel. The tumor cells are round to spindle in shape, have very little cytoplasm and contain small, fairly deeply staining nuclei. The cells about the peripheries are high columnar in type and have oval nuclei in the ends away from the stroma. Many of the tumor cell groups near their centers exhibit cells with vacuolization and small to moderately large cavities in which is a finely beaded material which stains homogeneously with eosin-like fine droplets of colloid. Some cells are in concentric layers like epithelial pearls. Some of these cavities are large and surrounded only with a rim

of tumor cells which are cuboidal rather than columnar at the periphery. Some of the sections show particles of bone in the stroma. Section from the block cut sagittally through a tooth shows a normal tooth outside the tumor.

MICROSCOPIC DIAGNOSIS. Adamantinoma.

In conclusion, I wish to express thanks to Professor F. B. Mallory for critically reviewing this article and the sections; to Mr. L. S. Brown, of the Massachusetts General Hospital Laboratory for his kindness in making the photomicrographs, and to Mr. Walter McCrocklin, a student in our laboratory, for the sketch drawn from the museum preparation of half the gross specimen and from the description in the laboratory records.

NOTE.—Since this article was written the boy reported five months after operation and showed no sign of recurrence.

THE PATHOLOGICAL AND CLINICAL ASPECTS OF THROMBO-ANGIITIS OBLITERANS.[1]

By LEO BUERGER, M.D.,

NEW YORK.

It is not my purpose to burden you with an extensive and detailed account of the pathological and clinical aspects of the disease thrombo-angiitis obliterans, because the clinical picture and the main facts regarding the pathological lesions are certainly sufficiently known to you. I shall attempt, rather, to present the subject matter from the view-point of one who has been fortunate enough to have had a large amount of clinical material at his disposal (more than 300 cases), from which all phases of the pathology and clinical course could be investigated.

Perhaps the best general view of the morbid process, the most thorough understanding and most satisfactory conception can be had by a general comparative consideration of the pathological lesions and their corresponding clinical manifestations.

If I were asked to formulate a general concept of thrombo-angiitis obliterans I should answer as follows: Imagine a patient seeking relief for acutely swollen superficial veins of the lower or upper extremities, of sudden advent, and with all the manifestations of an acute thrombophlebitis. Imagine this process involving a considerable portion of the distal territory of the internal saphenous vein, followed by abatement of symptoms, and consequent resolution or healing. You will be in no doubt as to the general pathology nor as to the clinical course of the condition,

[1] Read before the College of Physicians of Philadelphia.

though your estimation of the etiology will in most instances, at least, be obscure.

Transfer this picture to the deeper vascular system, over the distribution of the external and internal plantar arteries and veins, the dorsalis pedis, anterior tibial, posterior tibial, and the peroneal arteries and veins, that is, with lesions in territories where objective manifestations are absent—and you will be depicting to yourselves, what corresponds to my own conception of the pathological process in the disease, thrombo-angiitis obliterans. So here, too, we postulate an acute inflammatory and thrombotic lesion, but one involving deep arteries or veins, or both, as the initial stage of the pathological anatomy.

Whereas the patient afflicted with an inflammatory and thrombotic lesion of the superficial veins presents objective signs easy of recognition, the patient suffering from thrombo-angiitis obliterans in its earlier stages may offer no objective evidences suggestive of the true nature, or of the site of the lesion. It was but in a very few cases of my own series (more than 300) that I felt justified in ascribing certain symptoms to the incipient stage of the disease. Severe, non-localizable shooting pains in the calf or foot, attended with difficulty in walking, or, possibly, with tender calf muscles, with or without vasomotor symptoms and coldness in the foot, with or without obliteration of the dorsalis pedis and posterior tibial pulses, may be the only symptoms. It is only when we compare the history with the future clinical course and pathology that we can relegate such indefinite signs to the onset of the affection. In most instances, however, the patient will not seek advice for such initial symptoms, either because they are not sufficiently severe to require the attention of a physician, or because they are incorrectly regarded as rheumatic in origin, possibly due to trauma, cold, the presence of flat or weak foot, or because they are explained on the basis of some other minor ailment.

Strange to say, patients afflicted with thrombo-angiitis obliterans may present symptoms which differ in no way from those attending the thrombophlebitis of the superficial veins, or so-called migrating phlebitis. These are the cases of thrombo-angiitis obliterans in which an acute inflammatory thrombosis involves smaller or larger portions of the external or internal saphenous vein, radial, ulnar, median cephalic or median basilic vein. Such cases are the most instructive of all, for they are the ones which afford us material for pathological study. Here the veins are accessible; portions can be surgically removed when the lesions are in the acute inflammatory stage and submitted to histological examination.

While the former type of case is difficult to diagnose the variety with concomitant migrating phlebitis can be recognized by a

study of the vein lesions under the microscope. If the tissue be examined when the lesions are still in the early inflammatory stage, before organization or healing has taken place, certain characteristic and specific lesions can be identified, changes which I have elsewhere described as pathognomonic for thrombo-angiitis obliterans.

Having learned that the incipient lesion of thrombo-angiitis obliterans is an acute inflammatory one, involving the arterial and venous walls, we will expect an occlusive thrombosis as the immediate sequence, and will not be surprised to learn that this stage gradually gives way to one of organization and canalization, resulting in a healed product in which the vessel becomes converted into a cord, more or less adherent to its surroundings, in which even the neighboring nerves may become agglutinated and enveloped in fibrotic vascular cord.

It is the interference with the circulatory conditions of the limbs brought about by the extensive occlusive process that is responsible for most of the clinical manifestations of thrombo-angiitis obliterans. So that it may be safely said that patients afflicted with thrombo-angiitis obliterans do not suffer directly from the disease itself but from the disastrous occlusive thrombosis which signalizes Nature's method of healing a vascular lesion, that has long since disappeared.

From a study of the pathological material, and from a comparison of the lesion with the clinical history, we must conclude that insidious or clinically unrecognizable exacerbations of the lesion may occur from time to time, so that the involvement of the vascular territory with the obliterative lesion is a progressive one until the summit of the organized clot reaches the popliteal, in rare cases the femoral or even the iliac. It will not occasion astonishment, therefore, that the clinical manifestations, too, become more and more serious as time goes on.

Nor must we be surprised if thrombo-angiitis obliterans simulates clinical complexes brought about by arterial occlusion from other causes. Differentiation from arteriosclerotic gangrene, intermittent claudication due to arteriosclerosis, endarteritic occlusion, and other thrombotic conditions may at times be difficult. It is the fact that thrombo-angiitis obliterans occurs in *very young individuals* in whom both the *vis a tergo* and the cardiac power are adequate for compensation, and in whom the vascular adaptability is elastic in its scope—it is this fact that accounts for the seemingly almost inexplicable circumstance, that gangrene occurs *so* late, or may be absent, in spite of vast and extensive obliteration of arteries and veins. It is to the development of the collateral circulation, therefore, that we owe, in part at least, the production of a very peculiar, striking, and characteristic clinical picture, recognizable even though mani-

festations of the acute stage of the disease, or manifestations, such as migrating phlebitis, are absent.

CLINICAL SYMPTOMS.   I will not go into detail concerning the clinical symptoms, for they are sufficiently well known. It may be interesting merely to make brief mention of my own routine method of physical examination, one that has stood me in good stead, in the recognition and also in the differentiation of this disease from those other that closely simulate it, and then to illustrate by lantern slides the chief feature of the pathology of the disease.[2]

My own scheme includes the investigation of the following points: (1) the general appearance of the limb in the horizontal position; (2) in the pendent position; (3) the presence or absence of ischemia in the elevated position; (4) the estimation of the *angle of circulatory sufficiency*; (5) pulsation in the palpable vessels, iliac, femoral, popliteal, posterior tibial, anterior tibial, and dorsalis pedis in the case of the lower extremities, radial, ulnar, brachial, and axillary in the upper extremities; (6) the occurrence of *induced, reactionary rubor* or *erythromelia*.

1. THE GENERAL APPEARANCE OF THE LIMB.   Any departure from the normal should be noticed.   The presence of fissures, ulcers, perforating ulcers, bullæ, ecchymoses, impaired nail growth, gangrenous areas, signs of infection or lymphangitis or venous thrombosis, evidences of malnutrition, such as atrophy, exceptional prominence of the bony landmarks and extensor tendons, conservation or effacement of the normal irregularities of contour through edema or through thickening of the skin and subcutaneous tissues, are features of importance.   Variations from the normal color—particularly marked pallor in the horizontal position, a play of color over the foot, even in the horizontal position; cyanosis, increased redness—all these are manifestations of either impaired circulation or vasomotor disturbance.

2. IN THE PENDENT POSITION.   With the foot in the pendent position and in the absence of inflammation a red flush involving the toes and dorsum, as well as the sole of the foot, extending upward for a variable distance, rarely farther than the ankle, is a phenomenon that is characteristic of many cases and many types of reduced circulation due to vascular obturation.   This is a condition of *rubor* or *erythromelia* (Gr. *erythros* = red, *melia* = limb). It is brought about by a compensatory dilatation of the superficial capillaries, and is most characteristic of the disease, thrombo-angiitis obliterans, although also found in other arterial affections attended with closure of larger vessels.   It is frequently present in

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[2] The lantern slides are not reproduced in this paper; some have been published in previous papers on thrombo-angiitis obliterans.

arteriosclerotic and diabetic cases as well. It seems to be an effort on the part of Nature to make up for the impairment of circulation by virtue of dilatation and engorgement of the superficial capillaries. Although more striking in the pendent position the rubor may also be present in the horizontal position, and when continuously in evidence may be termed *chronic rubor* and *chronic erythromelia* in contradistinction to the *reactionary rubor* that may be induced by depressing the limb after previous elevation.

3. Ischemia or Blanching. This usually sets in rapidly when the affected limb is elevated whenever mechanical interference with the circulation is present. The extent of blanching and the rapidity with which it appears are both valuable aids in the estimation of the amount of obstructive arterial disease. When the affected limb is cold the tips of the toes may remain slightly blue or cyanotic. Should the blanching be slow in appearing, or very hard to determine, pressure upon the tips of the toes after the limb has been elevated for some time will demonstrate whether the part has become depleted of blood or not ("expression test"). Compression of the toes of the elevated foot in normal cases will reveal the presence of sufficient bright arterial blood (rarely slightly cyanotic), while a varying degree of ischemia, with or without marked cyanosis, will accompany obliterated or obstructed arteries.

4. The Angle of Circulatory Sufficiency. The estimation of this angle is based on the supposition that the normal limb, when elevated so as to be perpendicular to the horizontal plane, that is 180 degrees, still retains most of its color. When the circulatory mechanism is defective, and the limb is elevated to the vertical, a variable degree of blanching of the foot occurs. If the leg is then gradually depressed *the angle at which a reddish hue returns* (angle of circulatory sufficiency) will be found to vary considerably. In some cases it will be necessary to depress the limb to the horizontal before evidences of return circulation are manifest. The angle of circulatory sufficiency would then be 90 degrees. In many cases of arterial disease the estimation of this angle is a valuable adjuvant not only in the recognition of the extent of the circulatory disturbance but also in prognosis.

5. Absence of Pulsation as an Indication of Arterial Occlusion. We should be able to feel the femoral, posterior tibial, popliteal, and dorsalis pedis arteries pulsating in almost all individuals who possess patent arteries. In rare cases the dorsalis pedis may be aberrant in its course and therefore not palpable, or neither the dorsalis pedis nor popliteal may be accessible to the touch because of the stoutness of the patient.

To palpate the popliteal satisfactorily the patient is placed on his abdomen, lying prone. The leg is held at right angle, that is, vertical, the patient being asked to relax the hamstring muscles.

The artery is then sought in the upper half of the popliteal space, just outside of the semimembranosus and semitendinosus tendons, the fingers being pressed downward against the femur. In the upper extremities, the radial, ulnar, and brachial and axillary arteries should be examined for pulsation.

The absence of pulsation is, as a rule, an indication of occlusion at the point palpated, although in rare instances postmortem dissections have shown that the site of obliteration is somewhat higher up.

6. REACTIONARY HYPEREMIA, RUBOR, OR REACTIONARY ERYTHROMELIA. By this term we mean an *induced rubor* that manifests itself in the pendent position of the foot after the limb has been previously elevated to the vertical. It is a physiological phenomenon that ischemia, or blanching of a limb artificially produced by an Esmarch or Martin bandage, will be followed by sudden dilatation of the capillaries of the peripheral parts when the circulation is allowed to return. So, also, blanching will occur in a leg whose larger arteries are occluded on mere elevation 60 to 90 degrees above the horizontal without the use of any artificial means. When such a blanched limb is then depressed to the pendent position a similar induced or reactionary rubor will become manifest. This well-known manifestation may be invoked in the examination of cases in which impaired circulation due to arterial occlusion is suspected. It will be found particularly useful in cases of thrombo-angiitis obliterans, although also demonstrable in other cases of organic vascular disease. In early cases it is especially valuable, for it may be present long before the chronic condition of *rubor* or *erythromelia* develops.

With this introduction I may be permitted to give a brief survey of the pathology of the disease, pointing out the histological lesions characteristic of the various stages of thrombo-angiitis obliterans, and also calling attention to the facts that point to the inflammatory nature of the disease and to those observations that suggest that we are dealing with a process of microbial etiology.

In 1908 I pointed out that the name endarteritis obliterans as applied to thrombo-angiitis obliterans should be discarded, since the occlusive lesion is a thrombotic one, affecting arteries as well as veins of the extremities, and that it is independent of atherosclerosis or arteriosclerosis.

My investigations, which included a thorough pathological and histological study of the vessels in 45 amputated lower extremities, 1 upper extremity, and 25 pieces of superficial veins resected and exsected from the lower and upper extremities during attacks of so-called migrating phlebitis, have demonstrated that when the patient comes to the physician for observation the larger arteries, and often the larger veins, are completely obliterated.

As a rule the plantar vessels, dorsalis pedis and many of its branches, anterior tibial, posterior tibial, peroneal and sometimes the popliteal are already completely closed, although any one or more of these vessels may escape. One or both the venæ comites may partake of the same lesion. The obturating tissue is for the most part representative of or indicative of a healed lesion, or the end-stage of a process whose incipiency is marked by an acute inflammation of the vessel wall, with consecutive, red, occlusive thrombosis of the affected vessel. It is only in rare instances that the early stages of the vascular lesion are found in the deep vessels, but in superficial veins when they are affected with the lesion of migrating or thrombophlebitis, the early or acute stage of the disease can be studied.

GROSS PATHOLOGY. The deep vessels of the amputated legs regularly show an extensive obliteration of the larger arteries and veins. Besides this there are two other lesions which vary greatly in their intensity, namely, the peri-arteritis and the arteriosclerosis. The appearance of the vessels on gross section depends upon the age of the occluding process. Usually the vessel is seen to be filled with a grayish or yellowish mass that can be distinctly differentiated from the annular wall of the vessels, and that appears to be pierced at one or a number of points by an extremely fine opening through which a minute drop of blood can be squeezed. Such obturating tissue is firm in consistency and does not at all resemble the crescentic or semilunar occluding masses typical of arteriosclerosis. The vessel itself is usually contracted, so that its wall appears somewhat thickened. This picture is characteristic of arteries or veins which are the seat of a very old obliterating process, and is to be found most frequently in the peripheral portions of the vessels, although at times this type of lesion may extend throughout the whole length of the vessel from the dorsalis hallucis into the popliteal.

As we trace certain of the obliterated arteries or veins upward, we are apt to meet with a change in the character of the obturating tissue. Frequently it becomes softer, more brownish in color, and terminates abruptly in the lumen of an apparently normal vessel; at other times the brownish tissue gives way to soft, reddish masses which are evidently the results of recent. thrombosis. In some cases this thrombotic process occupies large portions of the vessel's course; in others it is of short extent and terminates in a long cone of recent thrombus.

The veins share equally with the arteries in the lesion of occlusion. In some cases the veins are more extensively involved than the arteries, and this is particularly true of the collaterals of the posterior tibial, which are often closed when the anterior tibial veins are open. As for the arteries, we usually find an obliteration of a part or of the whole of the anterior tibial; occlu-

sion of the dorsalis pedis, and dorsalis hallucis, of the posterior tibial and plantar vessels, with or without involvement of the peroneal. Sometimes the anterior tibial is practically normal in its upper half or upper two-thirds. More rarely a large portion of the dorsalis pedis is open, with the beginning of the occlusion in the upper part of this vessel or in the lower part of the anterior tibial.

Besides the lesion of occlusion there are two other striking changes, namely, a certain amount of arteriosclerotic thickening and peri-arteritis. Arteriosclerosis is absent in the younger cases; when present it is never pronounced except in those rare instances in which the patient has suffered from the disease for many years, and has reached the age of forty or more. As a rule, we note but a very slight degree of whitening or thickening of the intima, here and there, in the patent portions of the vessels. In a very few cases small atheromatous patches are present.

A much more interesting and more important change is the fibrotic thickening of tissues immediately about the vessels. Wherever the vessels are occluded there is apt to be an agglutinative process which binds together the artery and its collateral veins, and sometimes also the accompanying nerve, so that liberation of the individual vessels by dissection is difficult. The adhesive condition is due to fibrous tissue growth and varies considerably in its amount. The peri-arterial fibrosis varies, sometimes being almost absent, at other times so great that isolation of the vessels or nerves becomes impossible and the vascular structures make up one dense rigid cord.

HISTOPATHOLOGY. The lesions may be considered in two stages: (1) the healed or organized stage, and (2) the acute or incipient stage of thrombosis. Between the earliest alterations in the deep arteries and veins and superficial veins and the finished product there are a large number of intermediate pictures that illustrate the metamorphosis of the obturating clot into the intravascular cicatrix.

1. *Healed or Organized Stage.* The most common lesion is a total obliteration of the lumina of arteries and veins by connective tissue. Histologically this may be extremely varied in the general appearance, but each picture can be interpreted correctly as having its origin in the lesion of occlusive thrombosis. This obturating connective tissue usually harbors numerous small vessels, pigment containing hemosiderin, and a fair amount of connective-tissue cells. The canalizing vessels when they become dilated form smaller or larger sinuses, giving the fenestrated or cribriform lesion seen on microscopic section of the vessels, or when the canalizing vessel becomes eccentrically placed, and sufficiently large, this sinus is responsible for the appearances which have been incorrectly interpreted as the product of an endarteritis obliterans.

Elastic-tissue stains demonstrate characteristic differences between this process and arteriosclerosis. Thus the region of the organized clot is almost completely free from elastic tissue. The small amount which is present is concentrically disposed about the new-formed vessels.

Still more suggestive and instructive is the finding of various stages of the disease in different members of the same vessel sheath. Thus in one of the lantern slides shown a large artery affords a view of the old lesion as well as one of its venæ comites. Another accompanying vein, however, is in the "acute" stage of the disease, a smaller venule or satellite being in the intermediary stage, where certain "miliary giant-cell foci" make their appearance. Such pictures not only reveal the thrombotic nature of the disease, but also present an argument in favor of the following two assumptions: that the disease begins with an inflammatory lesion attended with occlusive thrombosis, and that it affects the arteries and veins in a sort of relapsing fashion, very much in the same manner as in the veins in migrating phlebitis.

The termination of the occluding tissue in arteries and veins is often seen in the form of a rounded, convex projection looking upward (cephalad) and lying in practically healthy vessel wall. At other times the old occluding tissue is capped by an additional clot which rises in pyramidal fashion ending by a long capering extremity.

2. *The Acute or Specific Lesion.* The early lesions are so characteristic histologically that their appearances are practically specific for thrombo-angiitis obliterans and may permit the pathologist to make a diagnosis of the disease. They are rarely to be seen in the deep vessels for the reason that patients do not allow amputation until the disease has lasted for months or years. However, they can be well studied when these are the seat of the typical migrating phlebitis, and have been shown by me to be identical with the acute lesions in the deep vessels.

The earliest changes appear to be the usual evidences of an acute inflammatory process involving all the coats of the vessel. The media, adventitia, and perivascular tissues are infiltrated with polynuclear leukocytes and the lumen of the vessel is completely filled with red clot. In the peripheral portions of the clot, larger or smaller foci of leukocytes (purulent foci) begin to form, whose growth occurs by virtue of immigration of leukocytes. Then certain peculiar giant-cell foci develop and are characteristic. They contain giant cells, endothelioid cells or angioblasts and numerous broken-down leukocytes. These foci then undergo connective-tissue replacement. The giant cells gradually disappear; numerous small vessels are formed, the final product being a fibrous nodule containing vessels and some pigment. In the rest of the occluding clot the organizing process is somewhat different, resembling

that which characterizes the organization of blood clot in other thromboses.

In short, the lesions in thrombo-angiitis obliterans are in chronological order: (1) an acute inflammatory lesion with occlusive thrombosis, the formation of miliary giant-cell foci; (2) the stage of organization or healing, with the disappearance of the miliary giant-cell foci, the organization and canalization of the clot, the disappearance of the inflammatory products; (3) the development of fibrotic tissue in the adventitia that binds together the artery, vein, and nerves.

A CONSIDERATION OF THE TREATMENT OF PERIPHERAL GANGRENE DUE TO THROMBO-ANGIITIS OBLITERANS, WITH REFERENCE TO FEMORAL VEIN LIGATION AND SODIUM CITRATE INJECTIONS.[1]

By Nathaniel Ginsburg, M.D.,

PHILADELPHIA.

The surgical treatment of impending or actual gangrene of the extremities due to pathological changes in the peripheral blood-vessels, termed thrombo-angiitis obliterans by Buerger, embraces a number of procedures which attempt to increase the circulation in the impaired limb. The successful application of a surgical principle to cure a pathological process presupposes the possibility of either totally extirpating the diseased area or structure, or the correction of a departure in normal organic function until such time as may be required for tissue restoration or regeneration to take place.

Buerger's convincing demonstration of the true pathological entity of the disease which bears his name leaves no doubt as to the presence of the extensive bloodvessel changes which have already taken place when these cases are first observed. In most instances the disease has progressed to the point of impending gangrene or actual digital death, and all surgical measures for relieving the great suffering and distress of these patients are really only palliative in nature.

A considerable amount of experimental laboratory work, performed abroad and in this country, for the purpose of establishing the value of arteriovenous anastomosis in the treatment of this disease, has proved rather conclusively that true reversal of the circulation in the affected limb cannot be accomplished, even though Carrell and Guthrie successfully established in their labora-

tory experiments the possibility of conducting arterial blood to the peripheral capillaries by way of the veins.

Arteriovenous anastomosis, femoral vein ligation, section of the sympathetic fibers about the femoral vessels, multiple ligations of the superficial varicose veins in the affected limb (Lilienthal), high amputation and intravenous saline injections have been proposed and performed by observers all over the world in their efforts to combat the circulatory failure in the affected limbs. In addition to these measures, every conceivable form of local treatment to stay the impending or spreading gangrene has been employed with almost uniform failure in the final results obtained.

Willy Meyer has recently contributed an important article upon the employment of conservative measures in the treatment of peripheral gangrene, and refers to the interesting work of von Oppel, who has performed femoral vein ligation in these cases, with the belief that the peripheral venous stasis thereby induced from the anatomical point of view has the same relative value as arterio-venous anastomosis.

This latter operation, often incorrectly termed reversal of the circulation in the affected limb, was first performed by San Martin Y Sastrustigui in 1902, and has been exploited by Coenen, of Breslau, Wieting, of Constantinople, and many others both abroad and in this country. The operation owes its conception to the successful end-to-end suture of bloodvessels practised by Carrell and Guthrie. As originally performed it consisted in an end-to-end anastomosis in Scarpa's triangle between the femoral artery and vein, attended by section of each structure and ligation of the proximal end of the vein and of the distal end of the artery. Later, lateral arteriovenous anastomosis of these vessels in the thigh was suggested by Bernheim and Stone, of Baltimore, with ligation of the femoral vein proximal to the site of the anastomosis as a necessary and important feature of the operation. As a rule the anastomosis in the thigh was made below the profunda femoris vessels.

The final results obtained and a study of the philosophy of this surgical procedure lead to the conclusion that the operation is founded upon a faulty anatomical and physiological basis. Guthrie has stated that he did not believe that arteriovenous anastomosis successfully applied to animals in the laboratory should be employed in the human being suffering from advanced vascular disease of the type under discussion. Stetten, of New York, in stating his views regarding the futility of arteriovenous anastomosis in the treatment of impending gangrene of the lower extremity, supplemented his condemnation of this operation by reporting convincing proof based upon injection experiments and dissections of the bloodvessels in amputated limbs. His studies have been confirmed by Horsley, of Richmond, whose conclusions are in unity

with those of Coenen and Wiewiorowski who likewise concluded, in 1911, that the operation was unsound and dangerous.

Stetten studied 136 published arteriovenous anastomoses, or attempts at this operation. He found that 30 deaths resulted immediately or shortly following the operation, and 11 patients died after amputation following the performance of the anastomosis. The immediate death-rate therefore was 30 per cent., and of those that did not die, 45 required amputation. Therefore in more than 72 per cent. of the cases arteriovenous anastomosis had either failed or could not be accomplished, owing to the technical difficulties encountered. Insufficient lumen of the vessels or advanced arteriosclerotic changes precluded even a successful attempt at bloodvessel suture in many of the failures reported.

If any value attaches to arteriovenous anastomosis it is probable that the good resulting from the operation is solely due to the ligation of the femoral vein on the proximal side of the newly created opening, thereby practically accomplishing in principle a pure femoral-vein ligation. Meyer has recently reported a case of Buerger's disease with involvement of the base of the big toe and adjacent metatarsal bone in which he performed arteriovenous anastomosis, with a good result. An analysis of the history of his case compares so closely with one of my own, in whom only ligation of the femoral vein was performed, as to make the cases identical from the stand-point of involvement and successful end-result achieved. In this instance the success attending the operation is credited to the so-called "reversal of the circulation" which is believed to have resulted.

No doubt there have been many failures following arteriovenous anastomosis for peripheral gangrene which have not been reported, and I can personally add to the long list of failures one of my own, of which no previous mention has been made.

It is apparent that arteriovenous anastomosis has no place in the treatment of this disease, since the high percentage of failures will always exist, owing to the technical difficulties attending the operation and the advanced state of the disease when the operation is performed. It must be borne in mind that while these patients suffer principally from peripheral vascular disturbances they are also poorly nourished and bear other evidence of a clinical syndrome of which their peripheral trophic disease is the most striking feature.

Femoral-vein ligation is a simple technical procedure and will certainly and effectively produce circulatory stasis, and thereby bathe the affected limb in more blood than is present when no retardation of the venous system exists. Since Buerger has shown that the principal changes are largely confined to the peripheral arteries the tissue asphyxia resulting from deficient oxygenation is not overcome by this operation. This operation has been per-

formed by von Oppel, Coenen, Lilienthal, Horsley and others and by myself in 4 cases. If desirable it may be done under local anesthesia. In effect, this operation has, no doubt, been performed many times, since the examinations after death, following arterio-venous anastomosis, have shown thrombus occlusion at the newly created bloodvessel stoma, or contraction amounting to a complete functional closure of the opening between the artery and the vein.

Independently, or in conjunction with this operation, the employment of intravenous injections of a saline solution, either 2 per cent. sodium citrate or Ringer's solution, has been carried out, following the suggestion of Kogo and Mayesima, of Japan. They reported 15 cases of this disease treated with injections of a saline without femoral-vein ligation in the surgical clinic of Professor Ito. Employing a viscosimeter for testing the blood they concluded that there is an increased viscosity in the blood of patients suffering from this disease. Based upon this observation came the conclusion to employ sodium citrate solution for intravenous injection in order to decrease the degree of viscosity.

Garbat, of New York, has recently stated and proved that multiple injections of 2 per cent. sodium citrate solution into the veins of the human organism do not have a deleterious effect, and I have also employed multiple injections of this solution in varying amounts in conjunction with femoral-vein ligation.

Other than the mere mention of a single case (Lakeside Hospital in Cleveland) I have been unable to find any reference to the results obtained by section of the sympathetic fibers about the femoral vessels. Many cases of thrombo-angiitis obliterans have as a concomitant feature of the symptom-complex pronounced vasomotor disturbances; but it is difficult to conceive how the advanced thrombus occlusion of the bloodvessels can be antagonized by . section of the vasomotor fibers surrounding the large bloodvessels in the thigh.

When one witnesses the excruciating pain which these patients suffer, with the attendant loss of sleep, often uncontrolled by sedatives, the temptation is quite strong to perform early amputation before or at the first evidence of peripheral digital death. Haste in amputating, without first employing conservative measures, will often sacrifice extremities which may have been saved. In many instances, even though palpable pulsation of the vessels is wanting, patients will carry limbs for years with lessened pain and arrested disease after one or more toes have been lost. If the process is rapidly gangrenous and conservative measures are contraindicated, early high amputation should be advised to obviate the greater dangers of delay.

These cases haunt the hospitals for months and years, and one surgeon will begin by amputating a toe, and after having visited

many institutions the final termination of the disease in the extremity or extremities involved will be high amputation by a surgeon in another institution. The first operation is not always the last, and if a follow-up system is employed in these cases, one is not surprised to learn that physical usefulness usually ceases with the early onset of the disease. One patient who came under my observation had had his first operation at the hands of Mixter, of Boston, fourteen years previously. Then followed successive operations by many surgeons in various institutions, and he finally entered Mount Sinai Hospital with two unhealed stumps a few inches below Poupart's ligament. Employing spinal anesthesia his long-continued suppuration was finally terminated. He had been an inmate of hospitals almost constantly since his first operation, and between his cigarette habit and the use of drugs to which he had become addicted, due to his great pain, he was in a restful state of mental apathy.

Another patient, whom I saw from the earliest physical appearance of the disease, a man, aged forty years, a carpenter by trade, suffered first the amputation of the toe of one leg, and then the leg itself was removed just below the knee, with long-continued suppuration and final slow healing of the stump, preserved for an artificial limb. A tourniquet was not required and there was scarcely any spurting from the tibial vessels when the amputation was performed. A year later he developed involvement of the big toe of the other leg, followed by slow and progressive involvement of the foot, refusing operation, until finally driven by the fearful pain in the gangrenous foot and leg to have removal of the limb in another hospital.

With reference to local treatment we have tried various saline foot-baths, heat, Bier's hyperemia, electrotherapy, and many drugs locally to the diseased parts, none of which have appeared to have any specific value. Much has been claimed for ascitic fluid applied locally to the involved digits. I personally have amputated limbs where free use of ascitic fluid was made and have never seen any benefit result from its employment.

During the period of life in which this tragic disease is commonly observed in the male adult the female is engaged in repeated pregnancies and thereby suffers from constant engorgement of the lower extremities as the result of increased pelvic pressure due to the gravid uterus. This might possibly be a factor of some significance in determining the discrimination of the disease in favor of the male sex. Most patients suffering from this disease are inveterate cigarette smokers, using a cigarette of cheap tobacco rolled in paper of very poor quality.

Among the causes assigned to the production of this disease are infection (Buerger), some underlying toxemia, and altered quality of the blood (Meyer). The determination of the causative factors

producing a disease of this type, having sharp limitations with reference to age, habits, nativity, and sex, calls for more determined and prolonged study in order to elicit a method of treatment more successful than any now at our disposal.

With reference to femoral-vein ligation the important facts in 4 cases are as follows:

CASE I.—W. K.; male, aged fifty-three years; Russian; fruit dealer; admitted to the Jewish Hospital May 21, 1916. Chief complaint: excessive burning pain in the right first and second toes. In December, 1914, the patient felt a burning sensation in the right big toe associated with constant severe pain, making sleep impossible. The toe became blue and extremes of temperature applied to the foot increased the pain. Electrotherapeutic treatment in the hands of the late Dr. W. L. Rodman improved his condition and the pain was lessened for a period of six months. In December, 1915, the pain and discoloration spread to all of his toes, involving the dorsal surface of the foot. Patient was born in Komnitz, South Russia, and came to this country when nineteen years of age. He began to smoke cigarettes when ten years of age, smoking ten to fifteen daily. He had typhoid fever at the age of sixteen; denies venereal disease; does not use alcohol; has worked hard all his life. He is married and the father of nine children, two of whom died in early infancy; the others are living and well. The winters are very severe in his birthplace, thirty miles from Odessa, and he was subjected to severe climatic exposure when he resided in Russia. Before he came to America he worked at a machine for about twelve years, employing both feet to run the machine. After coming to this country he peddled fruit for two years and then worked in a fish store, and finally went into the fruit business, being constantly exposed all this time to weather conditions. He has never been a big fish-eater.

Ten years ago, at the age of forty-three years, he was in the Jewish and Medico-Chirurgical Hospitals, the left foot having been amputated in the former institution for the condition which is now affecting his right lower extremity. This amputation followed multiple operations upon the foot for the relief of his condition. At the present time the pain in his right foot is persistent and unendurable without a sedative. The posterior tibial and dorsalis pedis arteries are not palpable. The mesial surface of the big toe at the first interphalangeal joint shows a trophic skin ulcer. The break in the skin is not complete. The nails of the first and second toes show marked trophic changes, the nail-bed of the second toe being the site of an ulcer of small dimensions. The dorsal veins of the foot are numerous but are fine and not distended, and the circulatory failure in the foot is marked by a line of cyanosis about 1 cm. proximal to the metatarsophalangeal joints, and the toes are mottled and cold.

May 22. 50 c.c. of 2 per cent. sodium citrate solution injected intravenously.

May 25. 32 c.c. of 2 per cent. sodium citrate solution injected intravenously.

May 26. 75 c.c. of 2 per cent. sodium citrate solution injected intravenously into the femoral vein, with coincident ligation of this vein by silk and catgut ligatures, with separate ligation of the long saphenous vein. The limb following ligation became deeply cyanotic, with intense mottling and marked diminution in temperature.

May 27. The appearance of the lower extremity is unchanged. The toes are intensely cyanotic, having a deep blue hue, and the foot is cold.

May 28. The leg is warm down to the ankle, with slight distention of the dorsal veins of the foot. The toes are less cyanotic, the blue color having given way to a purple-red hue, sharply defined at the metatarsophalangeal junction. The patient says he has less pain and slept better last night than any night since his admission into the hospital. Over the upper third of the leg there is some venous distention, an oblique vein crossing the tibia from within and outward and downward. The dependent position of the foot hanging over the side of the bed increases the reddish-blue hue of this part.

May 29. There seems to be more prominence of the dorsal veins of the foot and the color of the toes is assuming a normal red tone. The toes, however, are still cool and the lowered temperature of the part extends to the upper third of the leg. The nail-bed of the second toe is dried up.

May 31. 100 c.c. of 2 per cent. sodium citrate solution injected intravenously.

June 5. The foot is warm, there is little pain, and the venous stasis has completely disappeared. The toes are still discolored and reddish blue, but there is very pronounced improvement in the circulation of the foot.

June 6. 100 c.c. of 2 per cent. sodium citrate solution injected intravenously.

June 7. Patient's leg is much warmer, and he states that he feels less pain. Patient requested that further intravenous injections be discontinued, and at his request was allowed to go home. (Total 357 c.c. of 2 per cent. sodium citrate injected.)

August 4. The right leg is somewhat edematous, toes are cyanotic, tense, and uniformly involved in the disease. The dorsal surface of the foot is blue and very painful. There is no venous distention such as he had shortly after his operation, and apparently little permanent good has resulted from the operation. His pain has returned and is becoming severe, necessitating the constant employment of narcotics.

This case has been reported somewhat in detail because it is a typical example of a case of thrombo-angiitis obliterans relative to nativity, history, and onset of the disease, terminating in the loss of one extremity and the future loss of the other, following a total occlusion of the femoral and saphenous veins, with coincident injection of sodium citrate solution.

CASE II.—M. G.; male, aged twenty-seven years, operator by trade; born in Russia. Admitted to Mount Sinai Hospital May 8, 1916. Diagnosis: thrombo-angiitis obliterans of the left foot, with the presence of digital ulceration. He was treated for many weeks in the Polyclinic and Jefferson Hospitals without relief. The details of the disease are too time-consuming to enumerate.

May 11. Ligation of the femoral vein was performed below the point of entrance of the long saphenous vein. Marked venous stasis promptly resulted, assuming the startling appearance of the case previously reported. He received daily injections of Ringer's and sodium citrate solution in large quantities from May 12 to May 19 inclusive, when he refused further injections and left the hospital against advice. The social service worker following this case traced him to another hospital and reported that amputation of the leg was necessary, owing to the progression of the disease.

Case III.—J. E.; male, aged thirty-six years; Russian; baker by trade. Admitted to Mount Sinai Hospital January 10, 1916; discharged February 8. Diagnosis: thrombo-angiitis obliterans of left foot. Patient came to the hospital with severe pain in the big toe of the left foot, which became gangrenous, the gangrene extending to the tarsometatarsal junction corresponding to this digit. The acute process was of six weeks' duration, the toe becoming gangrenous two weeks previous to admission. Patient was an inveterate cigarette smoker.

January 10. Disarticulation of the big toe and the metatarsal bone was done; the wound was not sutured and no ligatures were required.

January 14. The wound was suppurating and gangrene was apparently slowly spreading; temperature, 100° to 102°. Patient discharged February 8, with a suppurating wound and marked failure in the circulation of the foot. He was readmitted to the hospital May 31 with an unhealed wound and discoloration of the remaining toes of the left foot. The toes and dorsal surface of the right foot likewise show circulatory failure. The dorsalis pedis artery is not palpable in either foot and the veins are small and not distended.

June 3. Femoral vein ligated, with coincident injection of 100 c.c. of 2 per cent. sodium citrate solution.

June 4. Left foot is much warmer than the right; the veins are congested and the patient states that he feels more comfortable. 100 c.c. of 2 per cent. sodium citrate solution injected intravenously.

June 5. Patient is comfortable.

June 6. Patient's left foot and leg are slightly swollen, due to the venous congestion produced by the operation. Extremities quite warm to the toe-tips, with normal color and very marked distention of the surface veins of the foot. The opposite foot (right), which has not been operated on thus far, is distinctly colder than the left, and is giving much pain and discomfort, with marked cyanosis of all the toes, the big toe being especially involved. In comparison the left foot seems considerably better nourished and the result of the ligation at this time is unquestionably astonishingly good in this case. The transformation seems almost unbelievable, and the patient is considering the same procedure in the right lower limb. He has slept better and is having practically no pain in his left foot.

August 1. Patient has been at work all summer, having little pain in the left lower extremity, which is markedly swollen, the edema having increased the leg to almost twice its normal size. The nutrition of the limb at the present time is good and the progress of the disease seems arrested. The wound resulting from the removal of the big toe and the contiguous metatarsal bone has completely healed. He is now suffering from involvement of the other extremity and the problem of treatment arises again in this case.

The patient was observed on October 3, and the examination of his left lower extremity showed considerable diminution in the size of the limb as the result of stasis resulting from ligation of the femoral vein. He is suffering practically no pain in this limb, and complains of pain and feeling of fatigue affecting the right lower extremity.

CASE IV.—M. T.; Russian; male, aged fifty-eight years; a truck driver in his native land, becoming a huckster upon his arrival in this country. Began smoking cigarettes at twelve years of age, averaging ten to twenty daily, and has been a heavy whisky drinker for many years. Married, had twelve children, eight of whom are living and well. Was in the Russian army for six years. Father died at ninety, mother at seventy-five. Family history negative in relation to the present disease. Ten years ago, when forty-eight, patient suffered from pain in the calves of both legs, compelling him to stop work at intervals. This pain continued until nine months ago, when his condition became so aggravated that he had to cease working. He has had a reddish-blue discoloration of the toes of both feet for the last six years and ulcerated areas over the anterior surface of both legs for the past five years, with failure of healing accompanied by great pain. The ulcers are trophic and pulsations in the vessels of the foot are absent. He was treated in the Polyclinic Hospital for six weeks by Dr. George P. Müller, who believed that the case was one of thrombo-angiitis obliterans, and submitted the patient to saline injections. This case was one

in which there was circulatory failure, but owing to the age of the patient and the atypical location of his trophic ulcers I do not know whether he can be termed a typical case of thrombo-angiitis obliterans, although the examination of both feet confirmed the proper classification of the disease as one of this type.

May 31. 50 c.c. of 2 per cent. sodium citrate injected intravenously.

June 3. 100 c.c. of 2 per cent. sodium citrate injected intravenously into the femoral vein, accompanied by ligation of this vessel. The leg immediately assumed an intensely purple hue, with a most pronounced venous stasis of the limb below the knee-joint. The patient was in a state of shock at the conclusion of the operation, with subnormal temperature and rapid pulse, and cried out because of intense pain in the limb.

June 4. Suppression of urine was marked, only one-half ounce having been recorded in the past twenty-four hours. The right lower limb is now mottled and markedly cyanotic below the knee-joint. The left leg still remains cold and blue. Anuria is complete, the patient having the odor of urine on his breath, is vomiting, and has a subnormal temperature.

June 5. Patient's condition remains the same. There is very marked or total venous obstruction of both lower extremities, suggestive of a thrombus of the inferior vena cava. Patient died on this day, apparently of suppression of urine.

He was a poor operative risk, and undoubtedly not a good case for femoral-vein ligation.

Femoral-vein ligation based upon the experience of these few cases is an operation of doubtful value, since only 1 of the 4 patients showed any improvement following its performance. This case has unquestionably improved to the point of security of the limb in which the venous current was obstructed. Involvement of the other leg is now taking place and the value attaching to the procedure may be still greater in the future, since it may preserve one of his extremities.

The operation is a hazardous one and may cost the life of the patient, as occurred in Case IV of my series. If ligation is done the ligature should always be placed below the entrance of the long saphenous vein into the femoral vein, thereby preserving some collateral venous circulation in the affected limb. Following this operation there is developed a large posterior femoral vein passing from the popliteal space as a tributary to the sciatic or inferior gluteal vein.

In one of my cases ligation had no effect whatever in retarding the progress of the disease, and even failed to produce venous stasis in the affected extremity. It was a convincing example of how greatly impaired was the arterial distribution to the peripheral parts in the affected limb, and proved that the problem cannot

be attacked except by dealing with the arterial element in this
disturbed circulation.

I believe that the poor arterial circulation present is much better
than the results attained by any of the proposed surgical measures
to increase the circulation in the involved extremity.

We must bear in mind that this disease is almost invariably seen
in its terminal stages and that surgical measures are simply palliative in nature and cannot achieve a positive cure. My own experience with the injection of the sodium citrate solution has not been
very satisfactory, since I have noted little improvement in the
patients, and have found it difficult to continue the injections over
a long period of time, since so little early relief has followed them.
This experience is in agreement with the later reports dealing with
the value of saline injections in this type of peripheral gangrene.
Much of the early improvement noted by other observers has only
been temporary, and lasting results have not been attained.

THE NEWER CONCEPTS OF THE NEUROSES: AN ESTIMATE OF THEIR CLINICAL VALUE.[1]

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I have tried to put to a kind of test some of the ideas concerning
the neuroses that have seemed worth while and have endeavored
to see what truth there is in them. In doing this I have attempted
to be unprejudiced and, as far as one may with clinical material of
a varied kind, to adopt a detached and unbiased attitude.

The questions I have set myself to answer are: (1) what are the
really important theories which cluster about the attempt to explain
the neuroses; (2) of what use are they; (3) what remains after the
untrue and useless are set aside.

What is to be understood by the term "neuroses?" They are
clinical pictures of diseases which are primarily psychogenic in origin
and in manifestation, the objective symptoms of which do not conform to the known laws of anatomical distribution or physiological
function, and in which the intelligence is not sufficiently affected
to be included within the limits of the psychoses, and in which conduct is kept within the limits of what is called normal.

This definition as set forth here is intended merely to delimit a
large class of nervous diseases from the organic on one side and from

the purely mental on the other, serving to section them off for the purpose of further discussion.

If certain general notions are kept in mind it is useful to think of such diseases as conforming to certain natural divisions into which they almost automatically fall.

The first of these notions is that a rigid classification is impossible and that pure types are rare.

The second is that certain of the neuroses deal chiefly with phenomena that are conscious and certain others with phenomena that are unconscious (or subconscious or foreconscious, whatever term is used).

In this sense the following tentative classification would seem to be of use:

1. Neurasthenia. A fatigue neurosis in which the elements of fatigue and irritability are the primary factors and in which all symptoms are capable of interpretation from these two points of view.

2. Hypochondrosis, in which all symptoms can be referred to perversions in interpretation of afferent sensory stimuli. To these the patient ascribes the evidence and proof of disease.

3. Psychasthenia, which is a congenital state of indecision and doubt, chiefly based upon the fear of the consequence of choice.

These three then are, according to this view, purely conscious in origin and manifestation. To their consideration the patient can bring his intelligence, his experience, and his insight.

4. Hysteria, in which there is a disassociation of consciousness, and in which the manifestation of disease are sharply separated from their origin, and in which conscious synthesis is wanting.

5. Compulsion neuroses, in which the force of an idea becomes the dominating factor in the patient's existence, driving him to the performance of acts contrary to his wishes and to his interest, and which by virtue of his struggle at neutralization or control, various phenomena result, such as fear, attacks of anxiety, etc.

Toward the orientation of these various types of neuroses four important sets of hypothesis have been adduced. They are in their order of importance:

(a) Freudian psychology.
(b) Janet disassociation of consciousness.
(c) Babinski group of ideas.
(d) The theory of congenital or acquired inadequacy.

In a rough sort of way the newer conceptions of the neuroses may be said to date from the time Janet, a trained psychologist, began to apply laboratory methods to the investigation of the neuroses in Charcot's clinic at the Salpêtrière.

From this clinic Freud received the impulse which led him to elaborate the psychological principles prevalent at that time. It was about 1900 that the result of this work began to penetrate into

the neurological world. No neurological epoch has been so fruitful in results and shown so much interest and effort on the subject of the neuroses as this period.

I am not concerned with origin or history, and it makes little difference whether to Freud or someone else credit or discredit should be given for the ideas which have aroused so much conflict. The names are therefore only important as they serve to identify this or that formula with which we are concerned.

By far the most ambitious attempt to solve the total problem of the neuroses is that of Freud. This attempt is concerned with the finding of a common etiology, the establishment of certain basic psychological principles—a mechansim of investigation which contains at the same time its chief therapeutic measure. In a paper of this sort it would be impossible to attempt any critical estimate of the Freudian psychology as such, nor does it seem to me that any approach to its final judgment in respect to its ultimate truth is at present possible. A system which aims at the psychological determination of so many aspects of mental abnormalities as this must, in the nature of things, contain many errors and wrong points of value. How much truth there is contained in it is, I believe, less important than how great is its usefulness and how frequently are its accepted facts capable of being put to the test of actual experiment.

It is obvious that a worker in the field of the neuroses need not be bound by any limitation set upon his activities in trying out a theory, so whether the proper Freudian attitude is present or not is of less consequence than that the usual critical atmosphere in any serious investigation be preserved. With this notion in view the first difficulty in the Freudian psychology makes itself felt by the lack of proof that the sexual etiology is common to all the neuroses. Granting as wide a conception of the term sexuality as is possible, the definite fact remains that there is found no such etiological uniformity as the Freudian literature insists upon. By no process is it possible to reveal a uniform and a persistent sexual etiology.

The sexuality conception of Freud may be very briefly outlined as follows:

In his early publications, from 1894 on, he divided the psychoneuroses that were due to sexuality into two groups: (1) neurasthenia and the neuroses of anxiety which were due to existing sexual troubles, and (2) hysteria and the obsessions due to sexual traumata of childhood period to the age of eight years.

In his later publications Freud seems to admit that too much emphasis had been placed upon these infantile impressions and that some of the histories obtained from psycho-analysis were imaginary. The sexual constitution of the infant now occupies a more important place and the term libido comes into prominence. According to this view the child has in him all the forms of sex perversion which

are met with in the adult, and is a polymorph pervert.   At the age of puberty the auto-errotic child transfers his sex objective to one of the opposite sex.

There are three forms that can be followed:

1. The infantile tendency may be perverted and be recognized by the object as a sex invert or pervert.

2. The infantile tendency is normal or otherwise and may be repressed and hidden by the object to crop up after puberty as a psychoneurosis.

3. The sexual tendency may be directed toward the purely psychical end in art, science, and mysticism, and this process is termed sublimation.

The technic of this investigation is usually that of psycho-analysis, developed by a thorough acquaintance as might be acquired through the literature, through contact with well-known Freudian students and by actual experience and study.   The criticism that is likely to be made to a negative conclusion of this kind is always based upon the insufficient technical ability with the method itself— a criticism which, unfortunately, can never be answered directly. To this conception this question can be put: Why is it if psycho-analysis has proved itself so excellent a device for the investigation of the neuroses, has proved its therapeutic worth so often, the mere fact that it does not in most instances reveal the expected etiology be taken as a proof that its technic is at fault?   It has been said that if the sexual etiology of the neuroses is not admitted that the whole Freudian fabric falls to the ground, and if in a psycho-analytical investigation of a case the sexual factor is not revealed, the proof is complete that the study has been made with a technic that is faulty and insufficient.   Such statements seem of less consequence than the fact that the method itself is of great value and has been responsible for a very definite advance in the investigation and treatment of the neuroses.

The criticism which confronts any attempt to delimit the Freudian doctrine from the point of view of its utility and adaptability is always based upon the fact that the critic is not an accredited Freudian and that he is not the technical master of the method itself.   I shall forestall this by frankly admitting both charges, with the plea that so valuable a body of doctrine must contain sufficient truth to admit of partial belief and partial mastery.

It is necessary to indicate now what are some of the other essential factors that form the so-called Freudian psychology.   As I have said, Freud has set himself the extraordinary task of building around the idea of sexuality and its perversions an etiological mechanism which should provide for all the neuroses a common causal impulse. This, it is to be understood, was in no sense a preconceived idea of Freud himself.   In the course of a series of cases studied by means of psycho-analysis he became convinced that this was true.   This

etiological conclusion would be considered as the most significant item in the list of necessary postulates of the Freudian theory.

Probably the next important fact would be the freely admitted proposition that practically all the neuroses, with the exception of the neurasthenic group, are unconscious or subconscious phenomena. As a necessary corelation to the etiology spoken of above, there has developed the important idea that, owing to the necessity of providing some means by which the sexual impulse may be controlled for the apparent benefit of the individual and society, a conflict develops through the mechanism of suppression. It is this conflict which is the logical consequence of the effort to keep back that which is not in harmony with the individual, or rather the conventional ideas of action and of thought, which civilization demands of him. Such group ideas, called constellation, associated with suppression of painful and emotional states, tend to be repressed or thrust back into consciousness. To this the term "complex" has been given. Such a complex tends to expression, and in so doing gives rise to symptoms which are at times the motor or sensory evidence of the conflict objectivated in the clinical picture known as hysteria.

These, then, form the third group of the essential formulæ of the Freudian doctrine. Sexual infantile trauma, repression with its great variety of mechanism, the establishment of the conflict, the notion of a complex and its need of expression, such an expression taking on the form of lawless and half-understood external manifestations. The fourth group of Freudian facts is the mechanism of investigation and treatment—that is, the psycho-analysis, which includes the use of the interpretation of dreams as an essential medium for the study of the repressed psychical material.

A discussion of psycho-analysis as a method need not detain us here, but the dream with its symbolic language and its interpretative value are of primary interest. To no part of the Freudian doctrine has greater significance been given than this, and by many it is regarded as Freud's lasting contribution to psychology.

Associated closely with the dream interpretation is naturally the conception of wish-fulfilment as an initiative of all dreams. There are many aspects of the dream problem which cannot here be mentioned, but a few are essential to keep the narrative thread of the discussion.

It is obvious that if a dream contains both repressed and unrepressed material the story of the dream is not so simple as the dreamer imagines. The content is therefore of two parts, manifest and latent. It is chiefly with the latter that the main interpretative effort is concerned. By a process identical with psychoanalysis the latent content is analyzed out with the object of seeing through such dream activities as condensation, distortion, overdetermination, displacement. These are terms used to express the manifestly absurd pictures with which dreams are filled. All

this seems to serve the purpose of defense, as it were, a protective mechanism to save the dreamer from the realization of what he is really dreaming about. Much of the language of dreams is symbolic in the sense that symbols are at the same time a mirror of infantile and primative speech and serve to express events and experiences incapable of personal conscious understanding. It is the interpretation of the symbolic language into terms readily appreciated which enables the interpreter to see very deeply into his patient's mind.

These, then, as I conceive them are the important facts in the Freudian psychology.

It is apparent that a method of investigation is of itself valuable only as it furnishes a mechanism by which truth can be reached, and that whether the final conclusion is always identical or not is of minor importance; but what does matter is the evidence of the value in suitable cases by the use of a method of this kind. Laying aside, therefore, the questionable nature of the root idea, included under the term sexuality, as limiting the aim and final goal of all psycho-analytic efforts into the neuroses, in what way are we the gainers through the immense labors of this band of enthusiastic investigators?

It might be well to call attention to one important fact which is commonly lost sight of when the neuroses are discussed; that is, with the closer study of the neuroses as mirrored in the Freudian literature greater attention and emphasis are necessarily given to the acquiring of data and to the study of the intimate mechanism of their occurrences. Paralleling this very important advances have been made in the technic of clinical investigation of organic disease as well. There results, then, two opposing tendencies, a clear and more definite determination of the neuroses, with the gradual subtraction from this class to this or that class of organic disease, and, on the other hand, a much more intensive effort directed to the understanding of the decreasing material included under the term neuroses. For example, the neurasthenic class has become enormously lessened by two important clinical points of view. The role of tuberculosis in causing fatigue states, which were formerly called neurasthenia, and the point of view which sees in many neurasthenias the prodromal state of various functional psychoses.

In this way the material open for Freudian therapy is capable of a good deal of warranted selection both as to type and to individual suitability.

The effect of all this effort may be easily seen in the histories of patients as they pass through the clinic or hospital service. Whether the neurologist or his staff are accredited Freudians or not there is to be observed a curious automatic insistence on the part of the clinical inquirers in regard to the presence of psychical traumata

in the past history of the patient. This inquiry does not stop with the ordinary conventional questions, it drives back into the realm of the patient's earliest memories. It is surprising, indeed, to observe how many facts are in this way obtained and how much richer the personal story of the patient becomes. I am referring not alone to hysteria, but to all classes of patients which this paper particularly addresses itself.

The conclusion seems irresistible, therefore, that the body of Freudian doctrine has penetrated largely into the general neurological mind irrespective of personal differences of opinions as to the correctness of many of its separate units.

This then may be regarded as one of the permanent results of what I called the newer conceptions of the neuroses.

Perhaps it means merely a sharpened intelligence and a more acute power on the part of the neurologist into the intricacies of his special problem.

The various results of psycho-analysis in different hands; its overenthusiastic supporters, jealous of any who do not conform to the strict rules laid down; its detractors, with their accounts of failure; and the intermediate group, patiently awaiting the light, make final judgment as to its permanent value a difficult matter to decide. Through it, however, much comes to light and many a case opens up to therapeutic possibilities denied to them before.

To summarize in a few words, Janet's conception of hysteria, psychasthenia, and other types of the neuroses is fraught with difficulty, and I do so only to keep this narrative in some kind of orderly succession.

It is interesting to know that Freud and Janet started out from somewhat similar points of view and have arrived at very different conclusions. This common point of departure is the notion of the disassociation of consciousness, the tendency of which is common to the type of neurosis which is called hysteria. There is a second curious point of similarity between these two investigators. Janet has attempted to do with his conception psychasthenia what Freud tried to do with the neuroses—that is, to collect under one head a great many different clinical types and associate them together with a common etiology, and by finding a common psychological mechanism, to consider them finally as slightly different types of one disease condition. Janet calls this psychasthenia, and Freud has done the same with the compulsion neuroses. Janet has assembled together such conditions in which doubt, fear, uncertainty, scrupulosity, etc., are the clinical expressions. In this way he has entirely separated them from dissociation states, etc., as represented chiefly in the hysteric group.

Janet's notion of hysteria best expresses this last idea. That it is a form of mental depression characterized by the retraction of the field of personal consciousness, with a tendency to the dissociation

and emancipation of the system of ideas and function that constitute personality.   To this is added the idea that in order that hysteria may be produced in any individual a definite state of depression or exhaustion of the higher cerebral functions is necessary. The lowering of the nervous strength produces in some manner a superficial retraction and an automatic state of depression.   Consciousness is no longer able to perform the more complex operations and becomes enfeebled for the time being. It thus becomes readily the subject of suggestive influence of all kinds.   The purely localized factor depends upon the additional fact that any function that has remained weak or disturbed is very apt to express itself in various abnormalities or arrested activities because it is the place, so to speak, of least resistance.   That is, whether the symptom should show itself in one or another portion of the body or in one or another function depends upon the fact that wherever the activity or mechanism has remained weak or disturbed in that very place the symptoms are expected to become evident.   In addition the more complicated a function is the more likely is it to become dissociated.   Such functions that were most active at the moment of emotional shock are the ones that are most likely to show the effect of the dissociative process.

These two sets of ideas appear to me to be the most suggestive and stimulating of the Janet psychology, or, at least, those around which, in a clinical way, efforts at understanding the neuroses may best be grouped.

There has been some effort made to point out the similarities of the Janet and Freudian concepts and to suggest that Freud simply elaborated the Janet theory of dissociation with the sexual etiology engrafted upon it.   Such efforts are fruitless, it would seem, at least from the point of view of a paper of this kind.

It is easily seen, however, that there is an identical point of view from which both men have chosen to start—that is, that the neuroses in their mechanism at any rate have this in common—the dissociation state of consciousness as a result of traumata with emotional consequences or accompaniments are of prime importance in the phenomena which afterward makes up the disease picture under whatever name we choose to call them.

Of the Babinski theory, which has particular reference to hysteria and to that alone, nothing is to be said here beyond mere reference to the well-known definition that it is a disease the symptoms of which can be caused by suggestion and can be removed by persuasion.   This, of course, is a formula, and Babinski evidently regarded it as such, and no more need be said of it than to point out its great value and the fact that it bears the weight of a very great neurological authority.

Without any attempt at elaboration I should like to refer very briefly to an idea which I am not sure should be associated with any

name, though to Adler is commonly attributed the credit of bringing it out. It is the theory of inadequacy. Adler is a representative of one of the secessionistic branches of the Freudian school, one of the earliest I believe to whom the Freudian yoke began to be rather heavy. In the maze of conflicting literary streams I have found it difficult to follow the development of his particular line of thought, so I have taken the liberty of thinking it out somewhat for myself— disclaiming, however, any idea of originality in the effort.

The idea I have in mind is that certain individuals apparently enter their conscious or interpretative existence with a feeling that almost all things that they are called upon to do are inadequately performed by them, or they find themselves inadequate to their performance. This state of mind can and probably does become unconscious, or perhaps after a time ceases to be recognized by the patient at all; but causes the most divergent symptoms, expressing themselves chiefly in an emotional background as states of depression, doubt, fear, etc. It is possible that certain congenital or acquired physical conditions play their part as well, and the struggle to which individuals of this type are naturally exposed furnish, it seems to me, a logical explanation of much that can later be interpreted from the various points of views which were touched upon in the preceding exposition of the theories which were considered.

With these four notions in view, laying aside many others which, for want of time, are not to be touched upon, let us attempt to briefly consider some of their clinical differences and doubtful phases.

Clinical Difficulties. Of the Freudian psychology there are three prime obstacles that stand in the way of their more universal use: (1) the uncertain character of what constitutes the essential facts; (2) the ever-changing conception of what is meant by its central idea, sexuality; (3) the technical difficulties which are placed rather arbitrarily, I believe, upon the procedure of psycho-analysis.

The restrictions placed upon the method itself and the material selected for its use are insisted upon with some exactness by the Freudian school, so that it is almost impossible to make use of it in any large clinical or hospital material. A complete psycho-analysis is a matter of many months, and perhaps can never be completed on account of the endless maze into which the psycho-analyst is lead and the necessity which he feels for obtaining as complete a collection of all the Freudian evidence as possible. The question of time, suitability, and patience restricts for purely Freudian investigations two types of the neuroses—hysteria and the compulsion types, the phobia, anxiety states, obsessions, etc.

It is a surprising thing to note how limited the material becomes in the face of the growing complexity of a therapeutic method and the doubtful selection of cases. Hysteria has become a rarity in clinical and private practice in proportion as our appreciation of its psychology has deepened.

For psycho-analytical study there remains, then, the group of compulsion types, and it is in this group that successes are most often met with. What psycho-analysis apparently accomplishes is not just what the Freudians would admit to be the definite goal of this procedure, but rather a curious interacting influence from physician to patient, less, I should say, by the filtering out of this or that feature of a Freudian history, but a more luminous view of the whole process, frequently, I am led to believe, unaffected by the idea of whether a true explanation has been reached or not. The pertinent fact remains in the patient's mind that there is an explanation and not the mystery that before enveloped him and his disease.

The Freudian psychology is a determinate thing, and as such gains immensely in therapeutic force. It goes, rightly or wrongly, to the root of the matter, and the patient soon begins to perceive the notion of the intellectual attack that is being made upon the disease which is tyrannizing over him to his discomfort and unhappiness. The unraveling, let us say, of the anxiety state by discovering that some traumatic experience of the patient's youth or infancy lies embedded in his consciousness dissociated from the proper emotional outlet and inhibited or repressed on account of the negative tonal background, is a great deal more significant to the sufferer, the idea, is, I mean, than is its discovery as a proof of the Freudian concept. It is in this conception in the patient's mind that this thing may be so, together with a realization of the complexity of the maneuvers necessary to arrive at such a conclusion that finally brings him out of the maze of misunderstanding into which he has become enmeshed.

The Freudian school is right in insisting that they are using a procedure of direct psychological determinism, and their opponents are wrong, I think, in asserting that their therapeutic results are gained chiefly by the influence of suggestion.

The cure or improvement of the neuroses is intellectual as is the method used, and the great strength of the Freudian school in my opinion is due chiefly to this fact.

For the neurasthenia I can see no place in the Freudian schedule, that is, if we restrict the term to the definition of fatigue states. Neither the masturbation nor the *coitus interruptus* etiology is convincing enough, nor does it fulfil a sufficient quantitative test to warrant a definite conclusion. These are episodes in many histories, it is true, but the patient remains unconvinced as to their prime importance, and to insist is to suggest, and to suggest is to deny one of the fundamental principles of the Freudian school.

But here, again, comes the great gain which we owe to the Freudian school. The neurasthenic is studied in a way that he never was before and by virtue of the tendency to minute analysis, which should be developed in all serious users of the psycho-analytic procedure, facts, experiences, emotional instances, curious byways in

the patient's life are patiently sought for until a more complete picture is worked out than the patient himself has any idea of. This turning into himself of the patient's scrutiny under the guidance of the psycho-analyst is of the utmost therapeutic importance.

The practical application of some of the Janet principles are less easily demonstrated. They are particularly adapted to rarer types of hysteria. It is a purely suggestive therapy in which hypnosis, or hypnotic procedures, are essential.

But here, too, the role of dissociation of consciousness and the important part played by traumatism in which emotional reactions are common qualities lead to a broader etiological outlook and a more careful search into the past of the patient. Of particular importance, I believe, is the Janet theory in the hysterical affections relating to the complicated mechanism of the special senses, seeing and hearing particularly. Here the dissociation is so obvious that the therapeutic effort at synthesis is unmistakably set out, and whatever the effort may turn out to be, whether of hypnosis, persuasion, reëducation, or training, the positive picture of the mechanism lends a great deal of force to the therapy which is applied.

So, too, in the psychasthenia class, when once we recognize the picture in this sense, we are prepared to give the effort a kind of realism, if I may use the word, which, without this application, would be, I fancy, totally lacking.

The patient's gain is obvious. To the intelligent victim of doubt, hesitation, scrupulosity, etc., a scheme of reasoning about his disease is a source of great comfort, and he feels upon much more certain ground when the mystery is somewhat removed and he can see to what end the therapy is tending.

The clinical application of the Babinski concept is less easily demonstrable, chiefly, I imagine, because it is after all a sort of formula, a kind of definition, and not a very convincing one at that. I should say its chief virtue lies in its prophylactic nature. No one can well doubt that in the realm of the traumatic neuroses it would have a certain application. Here the patient is very suggestible to all kinds of investigative maneuvers, and the neurologist, fortified with the Babinki formula, will attempt to get by with as little unnecessary examination technic as is possible. In such instances, for example, the patient if he be quickly isolated and studied with as little disturbance as possible, and the observation part be carried through with the utmost regard to avoid any element of suggestion, the chances are very good that no suggestive sympton will be developed.

The theory of inadequacy is chiefly illuminating not as a therapeutic procedure, but as lending a sort of understanding of possible protective agencies in a limited class of cases for which no obvious explanation can be found. Here, again, I believe, that the idea involved in this notion is of great practical value in the way of

broadening the horizon of the neurologist and lending a kind of easy plasticity in his approach to a case. This is rather difficult to set down in terms of abstract clinical value. To know about this thing is to give an additional grip upon a very complex clinical problem.

I have selected three instances for mention because they suggest what to me seems the great gain which much of the awakened interest in the neuroses is bringing about:

Case I has reference to a youth, aged about twenty years, with what is commonly called kleptomania.

Case II concerns a young woman, aged twenty-six years, the victim of an obsession.

Case III is concerned with a young man, aged thirty-four years, with what may be described as a contamination neuroses—a mysophobia.

I am sure you will understand that these are not to be regarded as clinical reports in any sense, but are simply very brief accounts to illustrate various methods of therapeutic approach, which, as far as I am concerned, would have been impossible without the work that has been outlined in this paper under the term—the newer concepts of the neuroses.

CASE I.—This boy was sent against his will to West Point. The discipline and the military atmosphere grew more and more distasteful to him until it seemed that life there would be unbearable. No way appeared open to him to get out, until he found upon reading a book of regulations that theft was considered a cause for dis missal. Gradually the concept took possession of him that if he were caught either in the act of taking things that were not his or if the things were found in his possession he would be sent away. In his locker some time afterward a variety of useless and valueless things were found—old books, pencils, worn-out shoes, etc., all belonging to his classmates. After investigation his resignation was asked for and he was sent home, a subject for neurological treatment, by the staff physician.

This boy asserted, and truthfully, that he was not aware that he had stolen anything, that he had no use for the things he took, and that he had no memory as to the time or occasion of his acts of theft.

The explanation of the case, that of a wish-fulfilment motive acting automatically and unconsciously proved not on y an adequate explanation, but brought the whole puzzling affair to the critical consideration of the patient. It satisfied the need in his own mind that his disease had a certain logical reason for existence, and with this end accomplished he was released from its influence.

The interpretation here sketched was based upon the use of many of the ideas suggested in this review, the carrying out of which took a long time, and the description of which has no place at the present.

Case II.—This case has reference to a curious obsession in a young woman which concerned the appearance in her consciousness of the figure of a young man whom she had casually met ten years or more ago. This obsessive fixation became so troublesome that depression, suicidal thoughts, inability to work, and other symptoms were making her life an impossible burden. Her definite assertion, over and over again repeated, that this man was a purely imaginary figure having no reference to the actual living reality for whom she had no interest, seemed at first conclusive evidence that the obsession had no particular logical relation to the effects which were produced. By means of interpretation of dreams it soon became evident that her explanation was a purely defensive procedure, intended to deceive the physician and herself, and that the fact was quite a contrary one. This enabled the problem to be put to her in its real relation, and with that most of the abnormal reactions seemed to disappear.

Case III.— This case has to do with the fear of contamination by syphilis on the part of the man previously infected, but now having through treatment reached what seemed to be a permanent negative Wassermann stage.

The man, very active in business, could no longer keep his position, a very important one by the way, on account of the fear that he would inflict with syphilis anyone who might touch anything that came in contact with him, such as letters, food, utensils, etc. It was found that the basis of his fear was that his mother would be the victim, and it was for her protection that he automatically withdrew himself from contact with the outside world.

He was sent to the Barnes Hospital, where by psycho-analysis and other methods a rich Freudian picture was gradually evolved, without, I may add, many of the embellishments so insistently demanded by the strict Freudian adherent to this type of neuroses.

This man is just now gradually getting about and is preparing to take up his work with the situation as clear as things of this kind can well be, and with his critical insight into the perplexing problem sharpened to a protective mechanism against the pull of his obsession.

With these three instances in mind I shall ask you to consider some of the conclusions to which the thoughts set down in this paper would naturally lead.

The point of view I have tried to assume is that the four theories here alluded to, and others not touched upon, contain in all probability some aspects of truth, though none contain all the truth. Therefore it is justifiable to pick out and select such as seem of use in the problems which the neuroses imply. The complex nature of the neuroses suggest the idea that no psychological system at present in vogue can explain enough of the total problem to warrant including all our therapeutic efforts at studying them under one head.

It is absurd, therefore, to speak of one as a Freudian, or this, or that, because it is freedom of choice and freedom of effort that is desirable and not the limitation placed upon one by the tyranny of one set of ideas.

There is therefore open to the choice of the investigator or thera-peutist of the neuroses the following ideas, some of which are capable of being used in the daily work of the neurologists and those who have occasion to treat the neuroses, and all of which have proved their worth by the test of actual experience.

1. The general admission that a psychologically intricate disease is to be treated by a psychologically planned theory.

2. No psychological system or device contains more than a por-tion of the truth.

3. Therefore it is justifiable to select as much of the truth out of any one system as seems worth while.

4. Psycho-analysis in the Freudian sense offers at the present time the most promising method of investigating and treating the neuroses.

5. The root notion of the Freudian psychology, that of sexuality, is to be regarded rather in the light of a hypothesis rather than a proved fact. The ideas associated with the terms repression, wish-fulfilment, infantile traumata, dream interpretation among the Freudian concepts are of practical everyday value.

6. As a working theory toward the explanation of hysteria and as providing a method of treatment of certain types of hysteria the Janet theory of dissociation consciousness is useful upon which to base synthetic therapy. In a negative way the Babinski idea of hysteria should constantly be kept in mind. The theory of inade-quacy furnishes to the physician a broad scheme of approach to many forms of the neuroses.

These seem to me therefore to furnish a broad general structure upon which ideas of causation and mechanism of the neuroses and direct therapeutic attempts upon the neuroses may be based.

These are things, pragmatically speaking, which the newer con-cepts of the neuroses have brought to strengthen the hands of the neurological therapeutist.

PRIMARY MALIGNANT NEOPLASM OF THE LUNG.

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MEDICAL literature has been extensively enriched by published reports on cancer of the lung. Whether this wealth of material is due to a greater efficiency in the domain of diagnosis or whether

pulmonary malignant tumors are on the increase remains at present a much-mooted question.

The difficulty which is encountered in attempting to establish an early clinical diagnosis of primary cancer is well known to the clinician, and is amply emphasized by many observers. This difficulty is probably due to the similarity between such a cancer especially in its earlier course and many other intrathoracic conditions, such as tuberculosis, unresolved pneumonia, pleurisy with effusion, pulmonary lues, and thoracic aneurysm. It is not uncommon even in our present-day knowledge to note in our professional literature, instances where the disease has been entirely overlooked, and the nature of the condition has been revealed only through an autopsy. Thus, Swan[1] reported the history of 6 cases who were sent to Colorado with a diagnosis of pulmonary tuberculosis, and the autopsy disclosed the true nature of conditions, all malignant intrathoracic tumefactions. Bromwell[2] relates a case of primary sarcoma of the lung proved by autopsy, which was previously demonstrated in the clinic as an advanced case of pulmonary tuberculosis, with cavity formations. Henrici[3] speaks of a case shown by autopsy to be a primary cancer of the lung in which the clinical diagnosis was unresolved pneumonia. In this case there was a persistency of high fever, delirium, loss of control of both urinary and anal sphincters, purulent and bloody expectoration associated with dulness in the right upper lobe. Many pneumococci and streptococci were found in the sputum. Tubercle bacilli could not be demonstrated.

My own series of primary cancer consists of 7 cases. Four of these have been verified by autopsy. Another was confirmed by operation. The fact is appreciated that although one cannot be absolutely certain of the diagnosis without a thorough necropsy, still it is fair to assume in the light of our experience in the other cases that clinical diagnosis corroborated by the roentgen-ray is certainly worthy of consideration.

In looking over the 7 cases we are confronted with the fact that 5 of them occurred in the male sex, and in 6 the initial lesion was on the right side. That seems to be the experience of other observers and those who wish to delve into the mystery of the etiology of cancer can certainly find here food for thought. The ages varied from thirty-eight to sixty-five years.

Pain and cough were the first symptoms in 6, while weakness and exhaustion constituted the prime reason that caused the other patient to seek medical advice.

Dyspnea was a very early symptom in all, and although at first it was only marked in some, after physical exertion it invariably

[1] Med. Record, November 15, 1913.
[2] Clinical Studies, Edinburgh, 1909–10, p. 284.
[3] Jour. Med. Research, 1912, p. 395.

became worse, so that later in the disease it actually amounted to orthopnea.

Expectoration was variable: in some very little, in others considerable. Monographs have been written on the sputa in pulmonary cancer, and all kinds of characteristic expectorations have been described. Some have even held that prolonged prune-juice expectoration is characteristic of pulmonary cancer, while the grass-green variety has been designated by others as the characteristic expectoration of pulmonary sarcoma. Those of us who have seen jaundice complicating pneumonia can verify Traube's observations that the grass-green variety is certainly not pathognomonic.

Hemorrhage was very common, and occurred in more or less quantities in 5 of the cases. Tumor cells were never found, although a careful and systematic search was instituted in all instances. We do not put too much faith in the diagnosis of so-called tumor cells, as polymorphous polygonal cells can be found anywhere in the respiratory tract.

Cachexia was a late symptom in all but 1 case. In this particular individual, referred to me by Dr. Battle, it occurred very early, and was associated with a profound anemia of the pernicious type. Sarcoma was our clinical diagnosis, which was corroborated by roentgen-ray examination. Unfortunately no autopsy was permitted by the family.

Fever was present in 3 cases, reaching as high as 105° in one individual. This was accompanied by night-sweats and chills, so that tuberculosis and abscess of the lung were very seriously considered.

Leukocytosis was present in every instance, varying from 10,000 to 20,000 per c.mm. There was nothing to be noted about the differential count, with the exception of the eosinophilia in the case referred by Dr. Battle, in which the diagnosis of sarcoma was sustained.

The above is a cursory summary of the symptoms; although persistence and progressive dyspnea, pain and dry cough out of proportion to the extent of physical signs in the chest, should always arouse suspicion of intrathoracic growths, nevertheless these signs and symptoms may occur in a variety of other respiratory lesions. At the first attempt to portray a clinical picture of pulmonary cancer it seemed an almost hopeless task, but on scrutinizing and studying the records of our cases we found a fairly well-defined syndrome, depending, as Stokes has remarked, on the anatomical disposition of the tumefaction.

Pulmonary cancer can be divided into three main clinical groups:

(a) Those originating in the pulmonary tissue, or, more correctly, in the alveoli, occupying more or less the whole lobe or even an entire lung.

(b) Those beginning in a larger bronchus and affecting those

adjacent portions of the pulmonary substance which are in the neighborhood of the hilum, involving and spreading from the root to the periphery. These cases, besides showing the symptoms of mediastinal pressure and of overcrowding the intrathoracic area, are accompanied by intense pains and embarrassment of respiration.

(c) Cancer, wherein the symptoms are marked by the signs of pleurisy with effusion, so predominant that the underlying cause is actually obscured.

As to the physical evidence, the first named presents a variety of classical signs. Change in percussion is not considered an early manifestation, but if light percussion is used, dulness or flatness will be elicited sooner than reported. Auscultation, however, in contrast to conditions in tuberculosis or pneumonia, will show a diminished breathing. Pleurisy with effusion can be easily excluded by the aspirating needle, and it is certainly suggestive of cancer if increasing dulness accompanied by diminished breathing occurs in the upper and anterior part of the chest. This peculiar combination is due, as a rule, to an obstruction of the bronchus by the tumor, causing an added atelectasis of that portion of the lung fed by the affected bronchus. As the tumor grows, degeneration of various kinds may make its appearance, irregular excavation will come about, and physical signs of percussion and auscultation will naturally change. In one of our cases we had all the signs of a cavity, such as metallic rales associated with tympany amphoric breathing. The diagnosis of tuberculosis and abscess of the lung was seriously entertained, but the absence of tubercle bacilli in the sputum on repeated examinations aroused our suspicions of a cancer. These degenerative processes are nearly always accompanied by nightsweats, high fever, and hemorrhages. Another auscultatory sign of great diagnostic value described by Behier and emphasized by Dr. Isaac Adler was the so-called carnage.[4] This is similar to the sound produced whenever the trachea is partially obstructed, and is heard in all classes of pulmonary cancers. This sign is sometimes noted in bronchitis on account of the plugging of the bronchus by tenacious mucus, but in contradistinction to cancer it is, of course, not persistent.

If the disease has lasted some length of time, demonstrable alterations in the thorax may be observed. There will be an asymmetry of the two halves, either in regard to their dimensions or to the degree of curvature. If the lesion attacks the lower or middle lobe, there will be, as in pneumonia and pleural exudates, divisions in the circumference of these parts; but if the upper lobe is affected, as more frequently happens, there will be an alteration in the thoracic arch. Of the first class the two following cases are somewhat typical.

[4] Adler: Primary Malignant Growths of the Lungs and Bronchi.

CASE I.—The patient, male, aged fifty-three years, was referred to me by Dr. Berlinger, November, 1914, with a history of having had grippe four years before. Since that time he had had frequent coughing spells, with expectorations, particularly in the morning. He was a junk dealer, and consequently inhaled much dust. On June 8, 1914, the patient for the first time expectorated blood; after that he had a number of hemorrhages, and stated that at one time he had coughed up as much as a cupful of blood and pus. He had frequent chilly sensations and afternoon fever. During the last three months he had lost fifteen pounds in weight. His appetite had been poor for six months. He complained of pain in the right side of the chest, in the region of the third and fourth rib, which had gradually been increasing. This pain had become so severe that it caused him to stop work in August, and he had not been able to resume it since. There was no history of tuberculosis or cancer in the family.

To recapitulate the principal complaints we found:
1. Pain in right side of chest.
2. Cough with copious blood expectoration.
3. Weakness and loss of weight.

Physical examination showed a much reduced individual; frequent coughing with expectoration; breath fetid; tongue coated. The glands in the neck were not enlarged. The pupils were equal and reacted promptly. The last phalanges of the fingers were clubbed and enlarged (pneumarthropathy). The pulse was 120. The respiration was 24 to 28; temperature, 99°.

Lungs. The anterior upper lobe of the right lung presented complete dulness from the clavicle down to the third intercostal space, and from this point downward the percussion sound was reduced. The same complete dulness existed posteriorly to a level of the sixth dorsal vertebra, and from there on relative dulness down to the base. The vocal fremitus was increased.

Auscultation of the anterior upper lobe showed breathing sound sub-bronchial in character. Posteriorly over the upper area, loud rales and sub-bronchial breathing were noticeable. Below the same conditions existed as anteriorly. Vocal fremitus was normal.

In the left lung only a few slight rales were heard. The heart sound was accelerated, low but clear.

The sputum was mucopurulent and mixed with blood; no tubercle bacilli and no tumor cells were found, but many flat epithelial and red corpuscles; few leukocytes; no hematoidin crystal.

The Wassermann test proved negative.

The urine contained urates and oxalate crystals.

The roentgenogram showed circumscribed shadow in the right upper lobe (see Fig. 1). On repeated examinations the same conditions were found. The temperature mounted higher in the afternoon, ranging from 99° to 105°.

The diagnosis of carcinoma of the lung with degenerative changes in the growth was made. On account of the agonizing pain the patient demanded relief, and was submitted to an operation, on January 23, 1915, at the German Hospital, by Dr. Willy Meyer.

A growth was found at the apex and upper lobe. The tumor had penetrated the pulmonary pleura and had grown diffusely into the surrounding soft parts. The tumor could not be eradicated. The patient stood the operation nicely, but twelve hours later developed pulmonary edema, to which he succumbed.
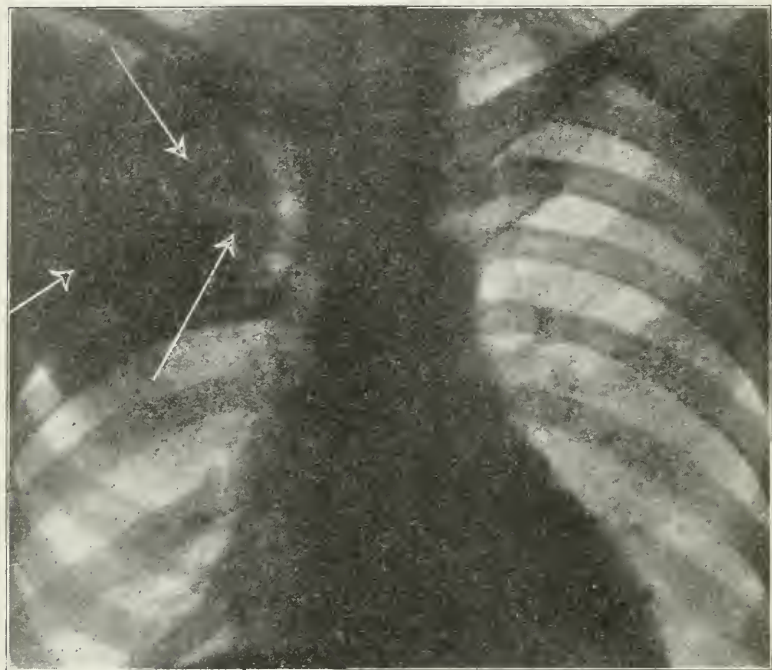
Case II.—Female, aged thirty-eight years, presented herself at the Polyclinic Hospital, complaining of cough and mucopurulent expectoration. During the last six months the sputum had become blood-tinged. There was neither family history of tuberculosis nor a pretuberculous infection. The pulse was 80, respiration 20, and temperature 98.6°. On inspection there was a dilatation of veins over the chest, more marked on the left side. There was also noted retraction at the left infraclavicular region corresponding to the third intercostal space. The percussion note and respiratory sounds were entirely normal over the right side, but over the left infraclavicular region there was dulness and resistance to finger percussion. The respiratory sounds over this region were faint and expiration somewhat prolonged. Voice and whisper were some-

what distant in sound. Percussion and auscultation of the remaining portion of the left lung were normal.

Because of the above-described signs over the left infraclavicular region, without involving the supraclavicular region of the same side, and because of the normal right side, a tentative diagnosis of tumefaction was made. This was supported by the normal pulse, dilatation of the veins, negative Wassermann reaction, and the absence of tubercle bacilli in the sputum in a number of examinations. Roentgenographic examination by Dr. Quinby at the Polyclinic Hospital revealed a circumscribed mass corresponding to the left infraclavicular region as indicated by the physical signs. The patient was observed for a number of weeks, with but little change in her general strength and physical signs. Since then the patient has not reappeared for examination.

In the second class of primary cancers, those which attack the root and hilum of the lung, a number of symptoms are noted, which are mainly due to pressure on neighboring structures. Closely allied to the resulting symptoms of this type of pulmonary cancer are the signs of thoracic aneurysm, esophageal tumefactions and enlarged mediastinal glands.

Venous obstruction with its picture of dilated veins of the neck, thorax, upper arms, and abdominal walls, associated with edema, is, of course, well known. Particular attention to the venos, azygos major, is paid by Roberts,[5] who cites the case of a boy, wherein at first a diagnosis of acute Bright's disease was made, because of general anasarca, etc., but later, after a more careful examination the effusion in the peritoneal cavity was found to be much less than the effusion into the abdominal walls and lumbar region. This naturally led him to the proper diagnosis, as these parts are drained by the intercostal and lumbar veins, which empty into the azygos major. One of my cases was considered by several clinicians as one of cirrhosis of the liver because of the so-called caput medusa and general abdominal edema. Here the peritoneal edema was quite insignificant as compared to that of the abdominal walls.

Respiratory obstruction by narrowing of the air passages was an early symptom in my cases.

The dyspnea is more intense, especially upon exertion, than in other pulmonary conditions.

Difficult deglutition because of an esophageal pressure is often experienced.

Pressure on the nerves in many instances may cause the first indication, leading the patient to seek medical advice. The nerves which are usually involved are the phrenic, the intercostals, the vagus, or the recurrent laryngeals and the sympathetic; thus irritation of the sympathetic may lead to an exophthalmos, or even more

[5] Lancet, December 21, 1912, p. 1714.

commonly to an inequality of pupils. Pressure on the recurrent laryngeal may lead to paresis of the vocal cords. Although in aneurysm this is a common sequel, affecting the left recurrent laryngeal only, in cancer, both recurrents as a rule are involved.

Pain in this class is extremely intense. The various distributions and intercommunications between the phrenic, the sympathetic, the intercostals, and the cervicals may cause a wide shifting of the referred pain to various localities. The sternum, nape of the neck, and the shoulders represent the most frequent sites. Roberts[6] calls attention to pericarditis as a symptom of mediastinal neoplasm. In my cases there was no sign of pericarditis, but Roberts maintained that pericarditis in the old is as pathognomic of mediastinal cancer as pericarditis in the young is of rheumatism. Besides these symptoms a more or less extensive area of dulness over the lungs must be present. In two of our cases these peculiar phenomena were accompanied by changes in the respiratory sounds. These zones of rapidly changing dulness are due to the atelectasis which is produced and followed by the lung becoming pervious to air again. Of the following 3 cases, which represent this second type of pulmonary cancer, the first will be described in detail. This case has already been reported by Dr. Adler in his monograph on *Tumors of the Lung* and by the author in the *Medical News*.

CASE III.—The patient (P. C.), aged fifty-five years, a cigarmaker, gave the following history: No trace of cancer or tuberculosis in the family. He denied lues and venereal infection. Five years previous to coming to our clinic he had experienced pain in the right side of the chest, with unproductive cough. Two years previous to his presentation at the clinic he began to suffer from dyspnea on slight exertion. The pain and the cough became more harassing, and the patient's expectoration became first mucopurulent and finally blood-tinged. On several occasions he had a genuine hemoptysis, with the expectoration of eight ounces or more of pure blood. There was no fever nor night-sweats, nor change in voice. The appetite was good, the bowels were regular, and during the entire course he maintained his normal weight. Physical examination revealed the following:

Fairly well-nourished man, with normal subcutaneous adipose tissue, 5 feet, 5 inches in height, and weighing about 130 pounds. The conjunctivæ were rather pale, and there was slight edema underneath the eyes. Complexion was somewhat livid. No enlarged glands could be felt in the cervical, axillary, epitrochlear, or inguinal regions. Both jugulars were enormously dilated and tortuous. Superficial veins of the chest and upper portion of the abdomen, especially on the right half of the trunk, were also greatly dilated and tortuous, standing out well above the surface of the skin and forming

[6] Loc. cit.

a huge caput medusa. A very slight superficial edema on the right chest was evident. The space above the clavicle was rather full. Respiratory motion was markedly reduced in the right thorax. Careful measurement of the thoracic arch showed no difference in diameter between the right and left side. Apex beat of the heart was not visible, but faintly palpable in normal position. Absolute flatness was found over the whole right chest, extending from the axillary line forward from the clavicle and downward beyond the sternum and emerging over the superficial area of cardiac dulness. Over this area pectoral fremitus was completely absent. The voice was diminished. The breathing was faint, distant, and sub-bronchial in character. There were no rales. On the portion of the lung adjacent to the dulness, expiration was harsh and prolonged. The right lung posteriorly and all of the left lung showed no essential changes. An aspirating needle introduced into the area of dulness seemed to enter solid material. The heart sounds were rather feeble, but there were no murmurs. There was no accentuation of the second pulmonary sound. Heart dulness did not extend beyond the left maxillary line. The radial pulse was fairly soft and regular and of the same volume on both sides. The liver and spleen were not enlarged; no abnormalities could be detected in the abdomen. Reflexes were normal.

The examination of the stomach contents after a test meal showed free hydrochloric acid and the absence of lactic acid. The tube went down with difficulty.

Blood examination made a few days later showed: Hemoglobin, 62 per cent.; red cells, 3,989,000; white cells, 14,000. Differential count gave polynuclears, 54 per cent.; lymphocytes, 34 per cent.; large mononuclears, 8.5 per cent.; eosinophiles, 3.5 per cent.; thus showing a preponderance of lymphocytes and a slight leukocytosis. Red cells stained evenly, but were not equal in size. Microcytes and pear-shaped cells were abundant, but there were no nucleated cells, no poikilocytosis, and no stippling. The repeated examinations of the urine showed no noteworthy change. Temperature was normal, pulse about 80, and respiration at rest 28. Numerous and most searching examinations of the sputum were made. At no time could tubercle bacilli, elastic fibers, or particles of tumor be found. Careful search for actinomyces, streptothrix, and other abnormalities proved negative.

From the facts just stated it seemed evident that we had to deal with some form of neoplasm involving the right chest and the anterior mediastinum, and compressing the large veins, most probably the superior cava. The fact that cough and pain in the right chest had been the first symptoms and had appeared five years before, and the further fact that, according to the patient's repeated statements and assurances, the dilated veins and edema were of comparatively recent date, necessarily led to the assumption of a

primary neoplasm of the right lung that gradually involved in its growth the anterior mediastinum with its contents.

In view of the long duration of the affliction and the comparative state of nutrition of the patient, the slight secondary anemia, the tardy involvement of the lymph nodes, we were inclined rather to exclude the more malignant form of sarcoma and to consider a slow-growing carcinoma or endothelioma of the lung as the most probable form of neoplasm in this case.

The patient and his friends were advised of the unfavorable prognosis, and he was especially warned of a sudden hemorrhage at any time endangering his life.

The patient remained under observation for two months, during which time the disease progressed with great rapidity.

Enlarged lymph nodes appeared first in the right axilla and then in the left, while the cervical and supraclavicular regions remained free. An area of dulness, with harsh and prolonged respiration and diminished vocal fremitus, appeared about the middle of the right lung posteriorly, together with considerable pleuritic friction. Very soon thereafter, with increasing dyspnea and distressing pain and cough, fluid appeared in the right pleural cavity, which rapidly filled.

The chest was aspirated and 20 ounces of clear serous fluid was removed. Almost immediately the pleural sac began to fill up again, but before the patient was ready for another aspiration he was taken in a carriage to a meeting of the medical society, at which he was to be demonstrated by Dr. I. Adler. On the way he was seized with a profuse hemorrhage which ended his life.

An autopsy was performed January 23, 1904, by Dr. Otto Schultze. From a macroscopic examination a tumor mass was found involving the lower end of the trachea on the right side, four rings above the bifurcation, and on the left side just at the bifurcation. This tumor continued and involved the right bronchus, reaching as high as 2 cm. above the origin of the innominate artery. Glands over the anterior portion on the right side of the dome of the pericardial sac were involved in the growth, and the upper lobe of the right lung was adherent to the sac. The growth extended directly through the anterior portion of the lobe of the right lung, following the larger branches of the bronchi to the costal pleura. The rest of the lobe toward the apex was atelectatic and the bronchi filled with pus. The middle lobe of the right lung was the seat of hepatization, very light in color and slightly granular. Wherever the growth pierced the wall of the bronchus to the mucous membrane the membrane presented an ulcerated and eroded appearance. The lower lobe was atelectatic. The diaphragm contained a number of villi markedly injected. The left lung contained a few grayish-white plaques (metastis), 0.5 cm. in diameter, on the posterior surface of lower lobe, on the posterior margin of the base and also on the

surface of the base. Embraced in the mass and constricted by it was the superior vena cava, showing a distinctly puckered arrangement as viewed from the right auricle. The right pulmonary artery showed longitudinal folds with a funnel-shaped narrowing down to the tumor, where the vessel is almost entirely compressed. The heart showed some brown atrophy, but was otherwise normal. The peritoneum was perfectly free. The spleen was small and congested. The liver was normal in size (surface smooth) and pale in color. The stomach and intestines were anemic but otherwise normal. The patient had but one kidney, horseshoe in shape, and ureters passing anteriorly.

The microscopic examination showed a typical flat-celled carcinoma in the primary growth as well as in the metastatic deposits.

Case IV.—David G., peddler, aged sixty years, complained of dyspnea on slight exertion, pain in the right chest and dry cough, all of which had begun about five years previously. These symptoms gradually became worse, and about two years before his entrance to our clinic his expectoration had already become blood-tinged and his dyspnea had become marked. His family history was negative, with the exception that his wife had died of carcinoma of the uterus. He denied syphilis and his Wassermann reaction was negative. A number of glands in the cervical axillary and epitrochlear regions were palpable and of firm consistency. The jugulars were dilated as well as the superficial veins of the trunk. There was a retraction in the right second intercostal space marked on inspiration. Percussion revealed flatness on the right side of the chest from the clavical downward and from the anterior axillary line inward toward the left merging into the cardiac dulness. Breathing was distant, sub-bronchial in character; fremitus and voice were diminished. The apex was invisible but palpable. The left side of the chest was normal. The heart sounds were feeble but regular. Tuberculin injections of 1, 3 and 7 mg. on respective days produced no reaction. An aspirating needle inserted in the flat area on the right side resulted in dry tapping. The temperature was normal on every occasion. Three months after his first appearance the patient felt decidedly worse, having lost about six pounds in weight and considerable strength. The chest examination showed now in addition to the signs noted previously, flatness at both bases. An aspirating needle now inserted in the eighth intercostal brought forth bloody fluid in considerable quantity. A gland removed from the supraclavicular region showed on microscopic examination a carcinoma. The patient's condition progressed rapidly, and he died shortly from pulmonary edema.

Case V.—A male, aged thirty-five years, white, referred by Dr. Battle, stated that he had been in perfect health until within four months ago, when he had begun to feel weak and to lose weight and strength. During this period he complained of cough and expec-

toration, which was at first mucous and later at times hemorrhagic. Dyspnea and intense pain localized in the interscapular region became marked. His temperature was 98.6, pulse 84, respiration 24. His skin was lemon tinted. There was considerable dilatation of the superficial veins anteriorly and posteriorly over the thorax. There was no enlargement of the lymphatic glands. Percussion gave flatness over the right chest, extending from the second intercostal to below the third anteriorly, and corresponding to the same posteriorly. The respiratory sounds were distant and bronchial in character; no rales were audible. Over the other parts of the right chest and the left chest nothing abnormal was disclosed. Roentgenographic examination showed a mass corresponding to the outlined area described. Blood examination showed a profound anemia. White cells numbered 12,000, with an 8 per cent. eosinophilia. No tubercle bacilli could be demonstrated. Complement-fixation for lues and actinomycosis was negative. The high eosinophilia, coupled with the apparently rapid course of the disease, impressed upon us that we were dealing with a primary sarcoma rather than a carcinoma.

The third or pleuritic type in my experience is more rapid in its course than the other two. It is extremely acute, and one is markedly impressed by its behavior. Suspicion of these cases is not aroused until recourse is had to several tappings. Aspiration never relieves, and the fluid, which is at first serous, rapidly changes in character through the hemorrhages. If the patient lives long enough it finally becomes chocolate color. Even after the tapping there is no abatement of the cough, dyspnea, expectoration, and general distress. The dislocated heart never returns to its normal condition. Exemplifying this type are the following two cases:

CASE VI.—Mrs. D., aged forty-one years, had been perfectly well until four weeks previous to her first consultation. During, this interval of four weeks she complained of pain on her left side, which was intensified on deep breathing. She suffered greatly from cough and difficulty of respiration. She said she had lost ten to twelve pounds during this short period. Her history included the fact that her mother had died of carcinoma of the uterus. Examination showed dulness over the left chest and flatness posteriorly. Breath sounds and fremitus were diminished. The heart was displaced to the right. Dulness reached as high as the fourth rib in the axillary line. On aspiration a serous fluid was obtained. The heart remained displaced to the right even after the tapping. Within three days the whole left side of the chest was flat. Aspiration was again resorted to and the return fluid was bloody. Repeated aspirations had to be performed in the next few weeks because of the difficulty in breathing, and in the later tapping the fluid had changed to a chocolate color. Edema of the lungs set in suddenly, with a fatal termination within five weeks after her first

consultation. Autopsy showed a left pleural cavity containing a considerable amount of chocolate-colored material. The lower lobe consisted of a complete airless, firm white mass. The middle lobe was soft and purulent and on section showed a cylindrical carcinoma. The right lung was edematous and hyperemic, otherwise by no means abnormal.

CASE VII.—Woman, aged forty-two years, was seen in consultation with Dr. Morgan. She was the mother of five children and had had typhoid twenty-five years before. Her personal and family history were absolutely negative. The patient stated that eight weeks previous while at dinner an amusing conversation had caused her to laugh excessively and started a cough, which remained unabated for three days, and which was not relieved even by opiates. According to her own knowledge this was the first evidence of cough she had experienced up to that time. Besides her cough, she now complained of weakness and dyspnea.

On physical examination the left chest proved absolutely normal, but at the right base posteriorly there was moderate dulness. Breathing sounds were distant and a few rales were audible. She continued in an unchanged condition, with a slight even temperature, for ten days. Her dyspnea then became intense and physical examination by Dr. Morgan revealed signs of pleural effusion in the right chest. There was cardiac displacement toward the left. The patient was transferred to St. Elizabeth's Hospital, where the dyspnea became exaggerated. Aspiration of the right chest showed bloody fluid. The heart did not return to its normal condition. Signs of pleural effusion returned in the next few days, after the tapping, and during the remainder of her life, which lasted three weeks after her admission to the hospital, several aspirations were performed. No tubercule bacilli or tumor cells were ever in the pleural fluid. The white blood cells count was 15,000. Her temperature during the interval in the hospital varied from 98° to 102°. Autopsy revealed an endothelioma of the base of the right lung with involvement of the right pleura.

In differentiating pulmonary cancer from other conditions, the anatomical distribution must necessarily be taken into account. If the disease attacks the lower lobe it can easily be taken for a simple pleurisy, especially in the early stages of the disease. Exploratory puncture in early carcinomas may be negative. But if a pleural effusion is present the fluid returns after tapping, and soon changes its character from a serous to a bloody or even a chocolate color. Percussion immediately after aspiration will still show in tumor cases a persistence of dulness. Again, as stated before, the heart even after tapping remains displaced in these conditions.

If the tumor occurs in the upper region tuberculosis must be excluded. It is well to suspect cancer in an elderly patient with cough and bloody expectoration if the tubercle bacilli are persistently

absent and the tuberculin tests are constantly negative. Dilatation of the veins and peculiar changing zones of dulness always point strongly to a tumefaction. In cancer you will again find that the dyspnea and the subclavicular pains are distinctly more intense. Again, in tuberculosis we have never seen a case wherein a great amount of tissue was involved on one side in which the other side was not affected to a more or less degree. In contradistinction to this, in primary cancer the other side is comparatively healthy, so that at least the physical signs of infiltration are certainly doubtful or absent. Again, if supraclavicular glands are present, excision should be resorted to and a specimen of the tissue submitted to the microscope.

With regard to aneurysm the roentgen-rays, which are of great service in the diagnosis of cancer, may be of little use in differentiating these two conditions. There are a few instances wherein the tumor lies upon the aorta and gives it an expansile character. It is not uncommon to have a difference in the two pulses in pulmonary cancer because of the subclavion pressure, which naturally adds to the difficulty in differentiation. Lung tumor though, according to A. Frankel, produces a double recurrent paralysis in contradistinction to the left recurrent paralysis which is usually associated with aneurysm. In cancer there is at times a distinct asymmetry of the thorax due to retraction of that side of the chest where the tumor is localized. The tumor, as it grows, frequently involves the pleura, prohibiting a proper expansion of the lungs. Absence of dulness over the lung and absence of any changes in the sputa would speak more for aneurysm or an exclusive mediastinal tumor than it would for a pulmonary cancer. A positive Wassermann reaction would point to aneurysm rather than to cancer. But it is well to remember that cancer and syphilis of the aorta or any part of the body may coexist. The writer has known of such cases of cancer complicated by luetic aortitis. Echinococcus cyst of the lung may be differentiated from cancer by the complement-fixation test. Roentgenography in differentiating these two conditions is of considerable value. Other pulmonary conditions which must be thought of include: infarct, syphilis, dermoid cyst, actinomycosis, chronic abscess and gangrene of the lung.

The roentgen-rays have considerably furthered the diagnosis of tumors of the lung. They are of considerable value in determining the origin and mode of extension. The commonest form seen by roentgenographers occurs in the upper lobe, where they produce an intense uniform shadow. This shadow does not quite reach the apex, and it may be difficult to distinguish it from other forms of infiltration. Other infiltrating growths may extend from either hilus into the lung field often merging with the diaphragm. Here fluoroscopic examinations in various positions will often differentiate these shadows from pleural effusions and tuberculous nodes by the density

and sharp contours. The bronchoscope has also been used as an aid to diagnosis, but its use at the present time is very limited. What the future has in store for this means of differentiation is a question. The treatment must necessarily, if radical, be surgical.

During the last few years intrathoracic surgery with its improved methods of anesthesia has been materially widened, and we feel that the patient suffering from this dreadful malady should at least be given the opportunity of relief by operation.

AN INDIVIDUAL QUANTITATIVE DOSAGE OF TUBERCULIN DETERMINED BY THE CUTANEOUS REACTION: ITS EMPLOYMENT IN THE TREATMENT OF SURGICAL TUBERCULOSIS.

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Tuberculin has been used more or less in the therapy of tuberculosis for the past twenty years. Various methods of determining the desirable amount for administration have been employed, some based on the reaction, some on the tolerance, and others on the opsonic index; but with them all there has been no way in which the severity of the reaction to be produced could be accurately controlled. The dosage has been arbitrarily fixed, and accordingly the effect has varied widely.

In all therapeutic measures, one of our ideals is the accurate determination in each individual case of just the quantity of the agent to be used, necessary to produce the desired result.

In 1910 White and Van Norman reported[1] an accurate method of determining, by means of the cutaneous reaction, the correct individual therapeutic dosage of tuberculin for subcutaneous injection This method they base on the varying sensitiveness to tuberculin of the surface cells of individuals with tuberculous lesions. They believe that the beneficial result obtained from the tuberculin is not due to the tolerance induced, but rather to the reaction of the body cells to tuberculin. No attempt is made to produce a tolerance. The individual quantitative dose is determined by the susceptibility of each patient to tuberculin, as shown by the cutaneous reaction. The desired quantity of tuberculin is that amount which will produce the greatest local, focal, and general reaction without producing constitutional symptoms. In this way one is able to use

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[1] Arch. Int. Med., October, 1910, vi, 449.

an effective, yet perfectly safe, initial therapeutic dose; the danger of overdosage, common to all of the other numerous methods in vogue today, is abolished. After a careful study of a large number of cases, White and Van Norman show that the quantity of tuberculin required to produce a cutaneous reaction of 4 mm. will, when introduced intradermically, produce an area of redness and swelling at the site of injection 2 to 5 cm. in diameter. This reaction they call the "minimal cutaneous reaction." In addition, they show that this amount of tuberculin is the desired quantity; that is, the amount which will produce the greatest local, focal, and general reaction without constitutional symptoms.

In order to make this arbitrary law applicable, it is absolutely essential to obtain accurately the quantity of tuberculin that will produce the "minimal cutaneous reaction" of 4 mm. In the cases upon which this report is based the technic used in determining the "minimal cutaneous reaction" has been practically that of the originators. As it is necessary to obtain absorption as readily as possible the solution of Old Tuberculin has been used. The flexor surface of the forearm is chosen for the initial skin test, since this allows the part to be kept in a comfortable position until complete absorption of the solution has occurred. The depth to which the scarification is made and its size are very important in order that the reaction may be accurately measured. The diameter of the scarified area should measure 2 mm., and its base should be definitely pink in color. No blood should be drawn. After cleansing the skin with ether two scarifications are made, one about 10 cm. above the other. A definite quantity, 0.01 c.c. of the tuberculin solution to be used, is then applied, by means of an accurately graduated pipette, to the proximal scarification which is used for the test while the distal one acts as a control. The solution is usually absorbed within half an hour, after which a protecting shield is placed over the area. Measurement of the area of redness and swelling is made at the end of forty-eight hours and seventy-two hours. The maximal reaction is usually reached at the end of forty-eight hours.

As many patients give a minimal reaction to 0.01 c.c. of a 1 per cent. solution of tuberculin, this percentage is used for the initial test. If 1 per cent. is found to be high a lower percentage is chosen, and *vice versa*, until that percentage is found which will produce an area of redness and swelling 4 mm. in diameter. This is the "minimal cutaneous reaction" of the patient, and the amount of tuberculin necessary for its production when injected intradermically will produce a local reaction 2 to 5 cm. in diameter. This then is the amount that is used for the therapeutic injections.

The solutions used for obtaining the "minimal cutaneous reaction," and for therapeutic injection, are made by diluting Old Tuberculin with sterile salt solution containing 0.25 per cent. phenol.

A constant volume is used for the therapeutic injections, so that 0.5 c.c. of the solution contains the desired amount of tuberculin.   For example, if 0.01 c.c. of a 1 per cent. solution, that is, 0.1 mg. of tuberculin, produces a 4 mm. reaction the solution for that particular case is made, so that 0.5 c.c. contains 0.1 mg. of tuberculin.   Fresh solutions are made for each therapeutic injection from stock solutions of higher percentages, which are kept on ice.

The injection is repeated every fourteen days in order that the patient may retain this reaction to tuberculin.   As a skin test is equivalent to a therapeutic injection it is better not to repeat the preliminary skin test for four or five days.   The therapeutic injection should not be given until seven to ten days after the skin test has been made, for if given at a shorter interval the local reaction is very likely to be much greater than desired.   After cleaning the posterior surface of the upper arm with ether the first therapeutic injection is given intradermically, so that by measuring the resultant local reaction the accuracy of the skin test may be checked. As the intradermic injection may cause some pain for the first forty-eight hours, subsequent injections are given subcutaneously, except that every two months the injection is again made into the skin, in order to determine whether or not the patient has changed in sensitiveness.   In none of our patients have we found it necessary to change the initial dose after it had been accurately determined.

A child, aged seven years, with marked bilateral cervical adenitis, was under treatment for twenty-one months, during which time the swelling and redness at the site of injection always remained between 3 and 5 cm.

A case of arthritis of the left hip after being treated six months improved and was lost sight of; after seven months he returned with a large abscess in the thigh.   His original dose of 0.05 mg. was injected intradermically with a resulting reaction of 3.25 cm., only 1 cm. less than the initial reaction.   Injections were not made when the temperature was above 100°.

Since its adoption in 1911 we have used this therapy very generally in surgical tuberculosis, the only contra-indications encountered and observed being a temperature above 100° F., or disease so advanced as to render any type of treatment of questionable value. The major portion of the operative procedures so generally employed formerly has actually been done away with.   The earlier experiences were detailed by Cashman,[2] and the present report is submitted in order to record our results since that time.   We feel that the results obtained justify us in a distinct feeling of encouragement, with reference to the possibilities in this somewhat dismal field, the more so by reason of the fact that with few exceptions our patients were ambulatory dispensary cases and obviously unable

[2] Am. Jour. Med. Sc., August, 1913, p. 213.

to alter the general conditions governing their mode of living to any great degree. In our cases tuberculin was not used as an absolute specific, but whenever possible in conjunction with the usual dietetic and hygenic measures. Special attention was given to the mouth, teeth, and tonsils in the cases with involvement of the cervical glands. Fluctuating masses were aspirated or incised when necessary. Sinuses were treated locally by dry dressing, application of tincture of iodin, and occasionally curettage. When joints were involved, extension and fixation were used. Operative procedures were limited as much as possible; for instance, excision of the glands of the neck, which formerly was common, has been only an occasional procedure during the last three years. The diagnosis was based on the physical examination, roentgen-ray pictures, negative bacteriological findings in cases with pus not exposed to secondary infection, the clinical history and microscopic examination of tissue removed. In the duration of treatment we were guided by the disappearance of symptoms and signs of activity at the site of the lesion. An attempt was made to continue the treatment for three months after the patient was apparently well and then to continue observation of the case for the succeeding three months. Most of the cases were taken from the dispensary, and unfortunately became irregular in returning for treatment just as soon as the condition improved. For the same reason the question of instituting proper dietetic and hygenic measures was very difficult, and in many cases impossible. As a result the majority of the cases received only the tuberculin and the limited surgical care outlined above.

In the present series there are 40 cases in which the dosage of tuberculin has been worked out by this method. The oldest patient treated was aged fifty-one years and the youngest fifteen months. Eight were below ten years of age, 15 between ten and twenty, 9 between twenty and thirty, 4 between thirty and forty, 1 between forty and fifty, and 1 above fifty. The largest individual dose of tuberculin determined in the series was 0.3 and the smallest 0.005 mg. This wide variation in the dosage corresponds to and emphasizes the wide variation in the sensitiveness of patients to tuberculin; the value in having a method whereby an individual quantitative dose may be obtained is obvious. The longest period of time over which the treatment was continued was twenty-one months in a case with extensve involvement of the glands on both sides of the neck and multiple sinuses. The long duration in this case was due in part to the fact that the patient was very irregular in returning; after the importance of regularity was impressed upon her and treatment could be systematically carried out the sinuses healed, the glands disappeared, and she gained in weight. She was discharged well, and when seen four months later was in good condition.

Over 500 therapeutic injections have been given, and in only one case were any constitutional symptoms observed.

A woman, aged thirty-five years, with marked pulmonary lesions and involvement of the axillary and cervical glands, was running a daily temperature of 99.5° before treatment was started; after the second injection the temperature reached 100.6°, with some headache and malaise. The tuberculin treatment was stopped and the patient subsequently disappeared.

Of the 40 cases herewith reported the greatest number had glandular disease, namely, 19 cases, all with the cervical group affected, 1 case showing evidence of involvement of the axillary group as well. Of the joints, in 6 cases the hip was involved, in 3 the knee, in 1 the ankle, and in 2 the wrist. In 4 cases the vertebræ were affected. The metatarsal bones and the phalanges of the hand were each diseased in 2 cases. The lesion was located once in the greater tuberosity of the humerus; 16 cases were open and 24 were closed.

Nineteen cases sought treatment because of cervical adenitis, 7 of them having sinuses. Of the 19 cases, 12 were discharged as well, 6 were improved, and 1 unimproved when last seen. By improvement we mean the closure of sinuses, decrease in the size of the glands, gain in weight, and general condition. Of the 6 improved cases, 2 failed to return after receiving six injections, 1 left the city after receiving two injections, and the remaining 3 are still under treatment. In the case classified as unimproved there was extensive bilateral involvement of the glands of the neck; ten injections resulted in marked gain in his general condition, the glands decreasing in size and his weight increasing 9 pounds. He then had an attack of acute tonsillitis, with increased swelling of the glands and return of pain. After the condition had subsided, tonsillectomy was advised, but the boy has not been seen since; in the light of his previous hostory it seems probable that removal of his tonsils and the continued tuberculin treatment would have resulted in great benefit.

A young girl with cervical adenitis submitted on two occasions to excision of the diseased glands. Following this, although dietetic and hygienic measures were used, the condition did not improve, there being, instead, loss of weight and impairment of her health. Finally, after determining the dosage by the "minimal cutaneous reaction," tuberculin was given; in a short time the glands decreased in size and her general condition improved with a gain in weight. She was discharged in excellent condition, weighing more than ever before, and has since remained perfectly well. No surgical procedure whatever was used in this case after she came into our hands. The average number of therapeutic injections given was 10, extending over a period of five months. This record in the treatment of tuberculous adenitis seems to us very gratifying. Numerous instances of striking and undoubted benefit could be cited, though perhaps the preceding case illustrates very well what may be accomplished.

We have had 6 cases of tuberculous arthritis of the hip; 1 case has been discharged as well and is now at work; 3 were improved and 2 unimproved. Of the improved cases, 1 is now under treatment. Another was treated three and one-half months, and the third, two months, when they failed to return. Of the unimproved, 1 received one injection and the other three injections. Of the 4 cases with involvement of the vertebræ, 2 left the hospital slightly improved and 1 without much noticeable improvement. The fourth is now under treatment and is improving. Abscesses were present in all these cases but one, and were either aspirated or drained.

In 3 cases the lesions were situated in the knee. One was discharged with moderate limitation of motion. The remaining 2 improved and were lost sight of. Of 2 cases involving the wrist, 1 is now well. There is limitation in motion, but no pain or swelling, and he has worked daily for the past three months. The second case disappeared after two and one-half months' treatment much improved. Two cases of metatarsal disease are now well.

Three additional cases will serve to show what may be accomplished in disease of the bone and joints. In a case involving the hip there was acute pain and inability to walk. Extension was applied to the leg, followed by fixation with a cast, when he was allowed to go home, returning from time to time for the tuberculin injections. This patient improved markedly and gained in weight, and was discharged four months ago. He is now working daily, and although he is only fairly well-nourished, he reports himself as perfectly well. In a case involving the wrist, with moderate destruction of bone, there was a very satisfactory result after tuberculin injections and fixation. Although the motion in the joint is limited the patient has been working in an office for three months. A case with disease of a metatarsal joint showed no improvement when treated by fixation alone, but when tuberculin therapy was instituted his condition rapidly improved and he is now able to walk comfortably without pain.

In Pott's disease the results have not been as satisfactory; however, in all but one of these cases the disease was well advanced, with the presence of large abscesses.

Throughout our series we have found that the results have varied in inverse ratio to advancement of the disease. Those cases in which abscesses or secondary infections were present showed slower improvement and less satisfactory ultimate results. The best results were obtained when tuberculin treatment was instituted early.

Of the 40 cases treated, 19 have been discharged well, 16 improved, and 5 have been lost sight of, with the condition unimproved. All of the cases which failed to show any improvement were under treatment for a very short time; as they were lost sight of before

any definite effect could be expected, we feel justified in excluding them in estimating our results. Granting this, there are 35 cases in which the treatment was continued over a reasonable period of time; of these, 19 are well and 16 improved. Of the improved cases, 7 are still under treatment. Our results also varied according to the nature of the tissue diseased. Tuberculosis of the soft parts responded more readily than those in which bones or joints were involved.

Of the 28 cases previously reported by Cashman, 11 were discharged as well and 11 improved, the remaining 6 being unclassified Including these 28 cases with out present series the tuberculin dosage has been obtained and the injections made by this method in 68 cases of surgical tuberculosis. Excluding the 11 cases which have been lost sight of we have 57 cases in which the treatment has extended over a reasonable period of time; of these 57 cases, 30 were discharged as well and 27 improved.

A series of 57 cases of surgical tuberculosis, even though they have been carefully followed, is perhaps too small to allow one to draw any definite conclusions. Nevertheless, in working with this number of cases for a period of more than four years one inevitably receives very definite impressions, and we have no hesitation in declaring that the impressions gained by us have been very favorable. As stated above, our operative work in this field has been greatly reduced, and we think replaced by a much improved therapy. We strongly urge a careful unbiased trial of the method upon those men whose work carries them into this field. These cases have been observed and treated in the surgical clinic of the University of Pittsburgh, and the thanks of the writer are due and gladly given numerous colleagues for help and encouragement.

THE RELATION OF THE RECENT EPIDEMIC OF RESPIRATORY DISEASES IN DENVER TO PULMONARY TUBERCULOSIS.[1]

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There have been under my continuous observation since November 1, 1915, 120 patients with pulmonary tuberculosis, of whom 20 were classified as incipient cases, 42 moderately advanced, and 58 far advanced. Of the first class, 2; of the second class, 9; of the third class, 12 contracted the prevailing respiratory infection, epidemic during the past winter.

The 2 incipient cases recovered completely without any sequelæ.

Of the 9 moderately advanced cases in 3 and of the 12 advanced cases in 5 there resulted an extension of their tuberculosis. Of the moderately advanced cases, 1 exhibited, four weeks after the onset of "la grippe," an albuminuria with granular and cellular casts, which condition was not present before. Of the far-advanced cases 3 present similar urinary findings without there having been previous evidence of renal disease; 1 far-advanced patient with albuminuria progressed favorably for about five days after the onset of his new infection, and then developed complete suppression of urine for thirty-six hours, and death followed in five days. I am satisfied that this new infection precipitated the functional collapse of his kidneys. One case with severe laryngitis and tracheitis now shows a definite tuberculous laryngitis.

This is a brief summary of the cases of tuberculosis complicated by "la grippe" which I have handled in the last three months, with a note of their complications.

The pathological investigations of Cornet, Babes, Evans, Schutz, Prudden and many others long ago demonstrated secondary invaders in the walls of cavities, even in miliary tubercles far removed from the original focus of infection. There followed the isolation and identification of these germs by the method first suggested by Koch, later applied by Kitasato, and now considerably modified and improved, namely, the washing of the sputum and the taking of cultures therefrom. Inoculation of laboratory animals with cultures taken antemortem and postmortem determined their virulence. Finally, the therapeutic test of vaccine therapy and the demonstration of immune bodies in the serum add other chapters to the story of mixed infection.

It is generally accepted that secondary infection in pulmonary tuberculosis does occur, and is serious, in spite of certain negative laboratory evidence, such as the occasional demonstrated avirulence of sputum isolated organisms and the curious anomaly in the field of comparative pathology, namely, that cavity formation is rare in animals with the exception of monkeys.

During or shortly after an attack of "la grippe" the physical examination may reveal apparently an alarming extension of the tuberculous process; however, the amount of damage often cannot be determined until some weeks have elapsed after the onset of the complication. Such a case I saw recently. A young woman returning from a visit home, contracted "la grippe" en route. Physical examination indicated a widespread involvement of the left lung from apex to base front and back and in the upper and middle lobes of the right lung. Two weeks later her chest returned to the condition presented three months previously: moisture in front on the left to the third rib only and half-way to the angle of the scapula behind; on the right, moisture to be heard only in upper lobe and interscapular region behind.

Granted that shortly after a severe attack of "la grippe" a consolidated lung rapidly disintegrates, that a comparatively slight infiltration becomes more extensive, and where a month ago there were slight changes in the breath sounds and fine and medium moist rales, today there are bronchovesicular breathing and large and medium moist rales, and instead of a symptomless, retrograde process, an actively, even rapidly advancing disease with all the evidences of marked constitutional disturbance; granted all these, what are the intimate details of the transformation? What chemically and biologically happens when simple caseation passes into excavation?

In the past year the work of Jobling and Petersen[2] upon the antiferments has thrown much light upon this question, and is worthy of brief consideration. In acute caseous pneumonia a large catarrhal exudate rapidly becomes caseous, with the death of many cells known to contain ferments, and yet no autolysis takes place. Jobling and Petersen contend that secondary infection results in softening because of the entrance of fresh ferments with the new invaders, and because the body fluids necessarily accompanying the new inflammatory condition dilute the ferment inhibiting substance and aid in its removal. They have shown that lipoids containing unsaturated carbon atoms are antitryptic in colloidal solution; that tubercle bacilli and tuberculous caseous material contain such lipoids; that the reluctance of caseous material to solution and absorption is due to the presence of these compounds; that the inhibitory effect of the antiferments is overcome when the unsaturated bonds are oxydized or satisfied with iodin. This work, in addition, gives a rational chemical explanation for the solvent effect of iodin on tuberculous and luetic tissue, and forms the basis, further, for a new theory of the origin of anaphylotoxin.

The organisms chiefly incriminated in this role of secondary invader have been the influenza bacillus, pneumococcus, streptococcus, and Micrococcus catarrhalis. The investigations as to the etiology of the current epidemic of respiratory infection in Chicago by George Mathers[3] would indicate that a hemolytic streptococcus was the causal agent. Williams and Burdick,[4] in Denver, have also demonstrated a streptococcus, and by most instructive work have proved the selective tissue affinity of the organism isolated.

John Ceconi,[5] medical inspector in the Division of Communicable Diseases of the Boston Health Department, has called attention to the great need of research along biological lines in epidemic respiratory diseases. He considers the influenza bacillus the etiological agent in the recent epidemic, although admitting the great difficulty

[2] Jour. Am. Med. Assn., 1914, lxiii, 1930. Jour. Exper. Med., 1914, xix, 251, 383, 459, and 239; ibid., 1914, xx, 321.
[3] Jour. Am. Med. Assn., 1916, lxvi, 30.   [4] Med. Record, 1916, p. 876.
[5] Boston Med. and Surg. Jour., 1916, clxxiv, 423.

in determining finally the causative organism from inoculated plates, upon which may be found more or less numerous colonies of other pathogenic organisms, such as the staphylococcus, streptococcus, and pneumococcus.

Luetscher[6] has not experienced this difficulty. After establishing proper conditions for collection of sputum for examination, he says: "It will be found that in acute conditions remarkable plates will result, and that, as a rule, one organism will be present practically in pure culture." It must be added that Luetscher's work related to non-tuberculous invalids and to non-epidemic infections.

Williams and Burdick[7] isolated a hemolytic streptococcus from the sputa of patients, demonstrated complement-deviation bodies in the serum, and finally inoculated an emulsion of this germ into the ear veins of rabbits. The rabbits killed forty-eight hours later showed definite tracheitis, laryngitis, and bronchitis.

There is not only disagreement over the nature of the recent epidemic, but there are conflicting reports from bacteriologists over the prevalence of certain organisms in the sputum and the relation of these organisms to the attendant respiratory infection—whether that infection be epidemic or non-epidemic in type. For instance, Lord[8] found the influenza bacillus in pure culture in 30 per cent. of his cases of lung infection in the interepidemic period. Luetscher considers the same organism, next to the pneumococcus, one of the most important infectious agents found in pulmonary lesions. "That it is not only present in pandemics and epidemics, but also the cause of approximately 30 per cent. of the pulmonary lesions in interepidemic periods."

Williams and Burdick, in a personal communication, state that during the past two years in over 500 sputum examinations, using human blood-agar as a medium, they have failed to secure a growth of the influenza bacillus in every instance. During this time the bacillus was grown only twice—once from material obtained from the submucosa of a case of atrophic rhinitis and once from a case of Ludwig's angina. They discovered the pneumococcus only nine times. Williams and Burdick classify the *Streptococcus mucosus* as a streptococcus, a classification which is not generally accepted. Hanes,[9] concludes that Schottmuller's *Streptococcus mucosus* is really a variety of pneumococcus. Its cultural characteristics, solubility in solutions of bile salts and its behavior in comparative complement-fixation experiments all support this opinion. Luetscher[10] found the pneumococcus the cause of 62.44 per cent. of all the non-tuberculous infections below the larynx, and together with the influenza bacillus, the cause of 90.94 per cent. of the infections of

[6] Arch. Int. Med., 1915, xvi, 657.   [7] Loc. cit.

[8] Boston Med. and Surg. Jour., 1902, cxlvii, 662; ibid., 1905, clii, 537 and 574.

[9] Journal of Experimental Medicine, 1914, xix, 38.   [10] Loc. cit.

the bronchi and lungs, 74.96 per cent. of the infections of the larynx and 31.29 per cent. of the infections of the nose, throat, and sinuses.

Cecil,[11] in a bacteriological study of infections of the upper respiratory tract, recognized the streptococcus viridans as the predominant organism in 56.2 per cent. of 89 cases non-epidemic in type.

It appears therefore that Ceconi, in Boston, determined the influenza bacillus to be the cause of the recent epidemic, while Williams and Burdick, in Denver, simultaneously found the influenza bacillus not a single time.

The consumptive is particularly liable to become infected during an epidemic, among other reasons because of mouth-breathing. This habit may have been contracted in childhood from adenoids or in later life from decreased lung capacity, nasal deformity, toxemia, fever, myocardial insufficiency, distorted mediastinum, or acidosis. In this connection it is interesting to note that Yandell Henderson,[12] of Yale, suggests as a test for acidosis the length of time the breath can be held More than once we have all been impressed by the fact that in advanced pulmonary tuberculosis, usually of the fibroid type, the patient is utterly unable to hold the breath. Occasionally a patient will have hyperpnea apparently out of all proportion to the lung involvement. Such a case will almost surely have a marked acidosis, whether this be due to a heart or kidney complication or to simple pulmonary tuberculosis, with or without reference to altitude. We may safely conclude that the tuberculous individual is prone to breathe through the mouth when from exerton there is unconsciously a need for more oxygen. Moreover, there is a manifest tendency to catarrhal inflammation not only of the entire respiratory tract but also throughout the alimentary canal. The consumptive, is in addition, a physical incompetent. The very first symptom of the disease perhaps was exhaustion. Fatigue and susceptibility to infection go hand in hand. An unpublished observation of Wade Oliver, of the Pathological Institute of the Cincinnati General Hospital, quoted by Woolley,[13] is that the blood taken from the veins of patients who were brought to the hospital in a state of fatigue, such, for instance, as following a debauch, is apt to show large numbers of organisms, especially those belonging to the group of hemolytic streptococci. Oliver thinks their source is in the pyorrheic gingivitides from which most of these individuals suffer. As the physical condition of the patients improves the blood becomes sterile. It has been shown, however, that the streptococcus viridans is the organism chiefly responsible in chronic and the hemolyticus in acute infections of gums.

There is good experimental evidence to support the view that the tuberculous patient has a specifically lowered resistance to the

[11] Arch. Int. Med., 1915, xv, 150.
[12] Jour. Am. Med. Assn., 1914, lxiv, 318.
[13] Jour. Lab. and Clin. Med., 1915, i, 45.

streptococcus and staphylococcus. Sakagami[14] reveals the interesting fact that the serum of tuberculous individuals has less bactericidal power on these organisms than normal serum.

Inmates of sanatoria and residents of the outlying districts of the city are less resistant even than the city dwellers. From the very fact of their isolation they lack the benefits of automatic vaccination that comes from frequent exposure or even repeated slight infections. Their position is somewhat similar to that of the Indians in the North Canada woods, to whom influenza and measles are real scourges.

I know of no experiments which have demonstrated by the use of an aerial route of infection that the organism responsible for the recent epidemic has a selective tissue affinity for the respiratory tract. Nevertheless, granted such a portal of entry, the habit of mouth-breathing, permitting the entrance of germs very much as the night hawk scoops in gnats, a susceptibility to catarrhal inflammation, a little exhaustion, perhaps suburban residence and long absence from exposure to the germs of mixed infection, and it is easily understood why the consumptive usually contracts "la grippe."

As a result of this complication I have recorded in the patients under my care 3 cases having a peculiar homogeneous salmon-colored sputum and marked laryngitis and tracheitis. Of these 3, 2 have cleared entirely and are as well now as before their attack. One case presents, one month later, a persistent huskiness with a definite tuberculous infiltrated larynx. It is not for me to take up the relation of simple laryngitis to tuberculous laryngitis. I will confine myself to a quotation from Lockard's[15] book on *Tuberculosis of the Nose and Throat:* "Acute laryngitis in the phthisical rarely induces the accession of local tuberculosis if the attack be promptly combated, but neglected attacks or frequent infection may, under fortuitous condition, lead to infection, or in healed lesions to a recurrence." Robert Levy, of Denver, from the wealth of his experience, has voiced repeatedly the same opinion.

Four cases not previously showing any evidence of kidney degeneration, developed during their illness a persistent albuminuria with granular and cell casts. It has long been noted that the consumptive apparently overcomes his lung trouble to die later of kidney degeneration. At any rate, we have all been impressed by the frequency of albuminuria in the moderately advanced or far-advanced cases, particularly in those who have been overfed for a long time. A patient raising daily two to four ounces of purulent sputum imposes an eliminative burden upon the kidneys which cannot be estimated, but must be very great. Barker[16] has called attention

[14] Lancet, 1916, i, 127.
[15] Lockard: Tuberculosis of Nose and Throat, 1909.
[16] Am. Jour. Med. Sc., 1913, cxlv, 42.

to the fact that the "toxic glomeruler nephropathies are often due to streptococcus toxins. The possibility of the complication should be thought of in every case of streptococcus sore throat, hence the general practitioner can do much in the way of prevention. *Every individual who suffers from sore throat, tonsillitis, or 'bad cold,' with fever, should be put to bed and be kept warm there until the infection is overcome.* Not only would much renal disease be thus avoided, but also many serious disorders of the heart and of the joints." Not only is it possible that the lungs may be infected secondarily by the streptococcus, either sporadically or during an epidemic, but it is extremely probable that the lung thus infected may become a focus for further metastasis to heart or kidneys. Parenthetically it may even be possible for the tuberculous lung to acquire a mixed infection from an abscess at the root of a tooth.

The *Bulletin* issued by the city of Philadelphia Board of Health says: "Don't forget that this disease"—la grippe—"may be complicated by pneumonia. It causes a profound depression upon the body, and is likely to affect the heart and kidneys."

Bonney,[17] in his book, *Pulmonary Tuberculosis and its Complications*, says: "There is ample clinical evidence to substantiate the belief that a prolonged secondary infection, though slight in degree, is sufficient to produce desquamative and degenerative changes in the kidneys of pulmonary invalids." Again, "Irrespective, however, of this consideration it is clearly demonstrated that kidney disturbances are much more common in those cases of pulmonary tuberculosis exhibiting varying degrees of secondary infection."

In the use of vaccines this established deleterious effect of streptococcic toxines upon the kidney must not be forgotton. In fact, the prolonged administration of any vaccine in anything but small doses may not be without considerable harm to the renal parenchyma. Longcope[18] by injecting egg albumen into animals has produced definite histological changes in the kidneys. That any anaphylactic reaction causes renal degeneration is not perhaps a warranted deduction from this work, particularly as it awaits confirmation. Nevertheless it adds one more warning against indiscriminate vaccine therapy.

The work of Travis[19] would indicate that milk proteins as such do not enter the circulation of severe cases of nephritis kept for some time on an almost exclusive milk diet. We do know that there are many cases on record of hypersensitiveness to egg proteins. The urine of patients ingesting many eggs may contain these proteins. Finally the tuberculous individual taking six to nine eggs daily and having a moderate trace of albumin, with many granular and cellular casts in the urine and losing weight, may upon the withdrawal

[17] Pulmonary Tuberculosis and its Complications, 1910.
[18] Jour. Exper. Med., 1913, xviii, 678.
[19] Annual Report of Health Officer of Port of New York, 1916.

of the eggs from his diet show a diminished quantity of albumin, fewer casts, and a corresponding symptomatic improvement.

In the absence of any specific remedy capable of routine administration in the treatment of tuberculosis, our main reliance must consist in making the patient take and assimilate a large, often a very large, amount of nourishment. From the ingestion, however, of twelve raw eggs, 84 grams of protein, one or two quarts of milk, 28 to 56 grams of protein, perhaps 3 or 4 cooked eggs, besides steak or roast beef, 40 to 60 grams of protein, together with a half-pint or more daily of extractives in the form of soup and beef juice, there should be afforded some idea as to the amount of waste nitrogenous matter the kidneys have to eliminate. Many patients compelled to take this amount of food are already laboring under a severe toxemia from the tuberculous process in the lungs, with perhaps an indolent superadded mixed infection. Given a patient so handled for six to twelve months, or longer it is not surprising there should develop an albuminuria coincidentally with an acute streptococcus infection of the upper or lower respiratory passages. I would not go on record as inveighing against forced feeding. It is invaluable at times. I am convinced, however, that a diet with two or three times the normal proteid standard continued for a long time may pave the way for the functional collapse of the kidneys at such critical times as those of acute severe mixed infection.

Time and space do not permit me to enlarge upon another very important phase of this subject—the possibility of damage to the heart. Reduction of the pulmonary vascular bed, toxemia, or distortion of the mediastinum by adhesions or other cause may severely handicap the heart in pulmonary tuberculosis. Certain it is that in acute articular rheumatism, scarlet fever, in fact in any febrile disturbance due to a streptococcic infection or associated with it, the heart may show sooner or later definite signs of myocardial degeneration. If the non-tuberculous individual should be protected against endocarditis and myocarditis when contending with a streptococcic infection, certainly the tuberculous invalid, whether we accept the theory of cardiac hypoplasia of older writers or not, is more than entitled to that same degree of protection.

Babcock[20] says: "The danger to life from such a degenerative process makes prolonged observation of the patient after convalescence from an attack of influenza highly important," and "not only is the function of the organ disturbed in the course of influenza, but signs of cardiac inadequacy may develop a considerable time afterward."

Recognizing early in November that a severe epidemic of "la grippe" was prevalent throughout the country, and feeling keenly my responsibility not only to my own patients but the many of

[20] Osler's System of Medicine, Lea & Febiger, 1913.

Doctor Bonney's under my care, I diligently and repeatedly admonished nearly all of them not to visit the moving-picture houses, the auditorium, the theatre, and other public buildings; to avoid the department stores above all places in doing their Christmas shopping. (As many as 35 to 40 saleswomen were sent home one day from one of the larger department stores of this city, with an estimated morbidity of 50,000 cases of "la grippe" in a population of 250,000.) They were urged, as far as possible, to keep off the street cars. Many were not allowed to go into the shopping district at all. All were forbidden to visit their friends ill with "la grippe," and were told not to receive any visitor with a bad cold or any recently recovered therefrom. Every patient, tuberculous or not, who contracted "la grippe" was promptly put to bed and kept there until every vestige of the acute infection had subsided.

One word on the subject of treatment after the acute stage: Specific treatment is now the vogue—perhaps not so much as a year or two ago, but still much resorted to.

I am inclined to think that one reason why vaccine therapy in mixed infection is so frequently unavailing is that the germs of the mixed infection have become so firmly established—"dug in," so to speak, in the walls of old cavities, large or small—that even though the serum may show a large content of immune bodies they are unable to reach the germs in sufficient concentration to effect their dislodgment. The walls of these old cavities are composed of tough old scar tissue in which tissue destruction and regeneration are at low tide and blood and lymph circulation stagnant. Phagocytic cells penetrate slowly this tissue and must meet the invading germs improperly supported by immune bodies and with their activity limited, perhaps by age and certainly by their environment. The natural resistance of the tissue cell is low at the immediate point of attack. In these cases the invader acquires such resistance to the defensive powers of the host, and the latter such resistance to the harmful effect of the invader that a prolonged condition of infection ensues—what Hans Zinsser calls a "sort of truce without manifestation of disease?" until a repeated infection perhaps carries off the patient.

The great lesson of this recent epidemic is not whether the causative agent, is a streptococcus that does or does not ferment this or that carbohydrate, but that we and our patients are periodically exposed to a malady of great contagiousness, caused this year by a streptococcus, perhaps next year by a pneumococcus. At any rate, the infection is produced by a germ with whose biological characteristics we are for the most part unacquainted. When it becomes apparent that such an epidemic is upon us, stringent prophylactic measures should be instituted, including the isolation of all cases. The causative organism should be identified, following which it is important that its tissue affinity be established and serological

experiments instituted, to the end that we may know, not so much what value may be placed upon curative vaccine therapy but what protection we may expect from prophylactic inoculation. We should know whether general antigrippe inoculation is feasible.

Other organisms must be studied along lines laid down by Cole[21] Dochez[22] and other workers[23] [24] [25] in the Rockefeller Institute in the case of the pneumococcus and by Martha Wollstein[26] in the case of the influenza bacillus.

In conclusion, in pulmonary tuberculosis "la grippe" may prove a fatal complication—the last straw that breaks the back of his resistance—by establishing in the lungs an ineradicable secondary infection with its attendant dangers—by inflicting upon him that dreaded complication, tuberculous laryngitis, by causing the collapse of already overburdened kidneys or weakened heart.

It is incumbent upon us therefore to protect to the last degree the tuberculous invalid from this epidemic form of respiratory infection.

ANALYSIS OF THIRTY CASES OF PULMONARY TUBERCULOSIS TREATED BY THE INDUCTION OF AN ARTIFICIAL PNEUMOTHORAX.[1]

By Paul H. Ringer, A.B., M.D.,

ASHEVILLE, N. C.

In this paper it is my intention to abstain wholly from details of technic and to present that in which after all we are most interested, the results of treatment.

It need merely be mentioned that by the induction of an artificial pneumothorax it is sought to compress the lung in an "air splint," this air splint consisting of nitrogen gas allowed to flow between the parietal and visceral layers of the pleura; and that by maintenance of this compression and consequent absolute rest to the damaged organ for a period of time varying from six months to three years it is hoped to obtain cicatrization and healing of the diseased lung. Cases suited for this treatment are either those that are wholly unilateral or those with severe involvement on one side and comparatively insignificant disease on the other.

In my work I have used exclusively the puncture method of

[21] New York Med. Jour., 1915, ci, 1 and 59.

[22] Jour. Exper. Med., 1912, xvi, 665.

[23] Dochez and Gillespie: Jour. Am. Med. Assn., 1913, lxi, 727.

[24] Bull: Jour. Exper. Med., 1915, xxii, 457, 466 and 484.

[25] Gay and Chickering: Jour. Exper. Med., 1915, xxi, 389. Chickering: Ibid., 1915, xxii, 248.

[26] Wollstein: Jour. Exper. Med., 1915, xxii, 445.

Forlanini, inserting the needle through the different layers of tissues until it was seen by the characteristic negative fluctuations of the water manometer with which the needle was connected that the eye of the latter lay between the pleural layers. With the needle carefully held in this position the manometer was turned off and the gas turned on.

The cases treated by this method have all been advanced cases with the exception of 4. In 3 of these pneumothorax was induced for the purpose of stopping persistant bleeding, and in the
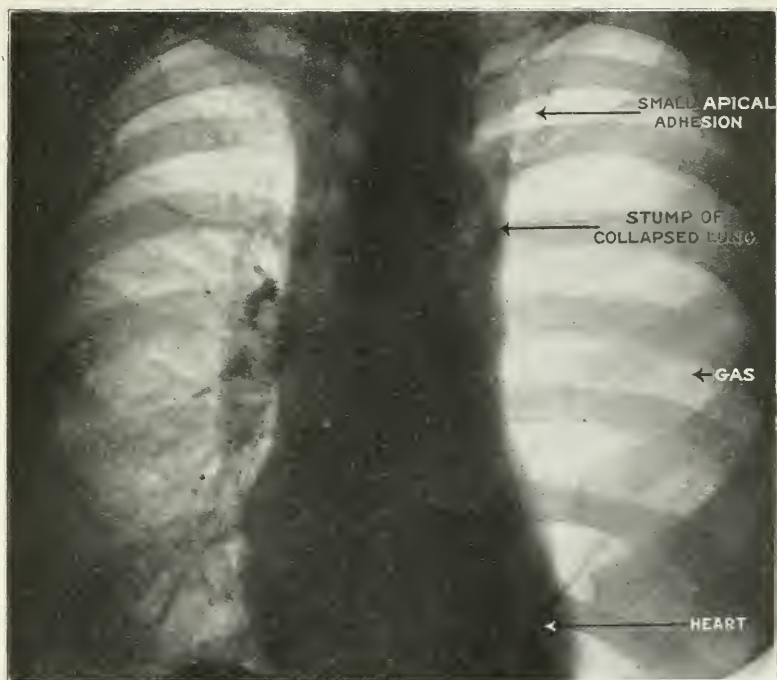
FIG. 1.—Successful left-sided collapse. (Miss A., July, 1913.) Patient well; has resumed household duties; lung has recently been allowed to reëxpand without the onset of any bad symptoms.

fourth case to check a rapid spread of disease from an apparently small focus. Some of the cases have been wholly unilateral; the majority has been bilateral with by far the greater amount of involvement upon the side it was sought to compress.

In the past three and a half years the procedure has been tried in 30 cases. I have grouped my results under five headings:

1. Complete success, 7 cases or 23.3 per cent.

2. Complete success for stopping hemorrhage, 3 cases, or 10 per cent.

3. Partial success (gas still being given), 2 cases, or 6.6 per cent.

4. Prolongation of life for an appreciable period of time, 4 cases, or 13.3 per cent.

5. Failure, 14 cases, or 46.6 per cent.

If headings 1 and 2 are considered together, the percentage of successful attempts is raised to 33.3 per cent.

In the cases coming under heading 1, there resulted a complete cessation of or a very marked diminution in all symptoms. Temperature became normal, cough and sputum disappeared wholly or almost so, and the patients gained strength so that they were
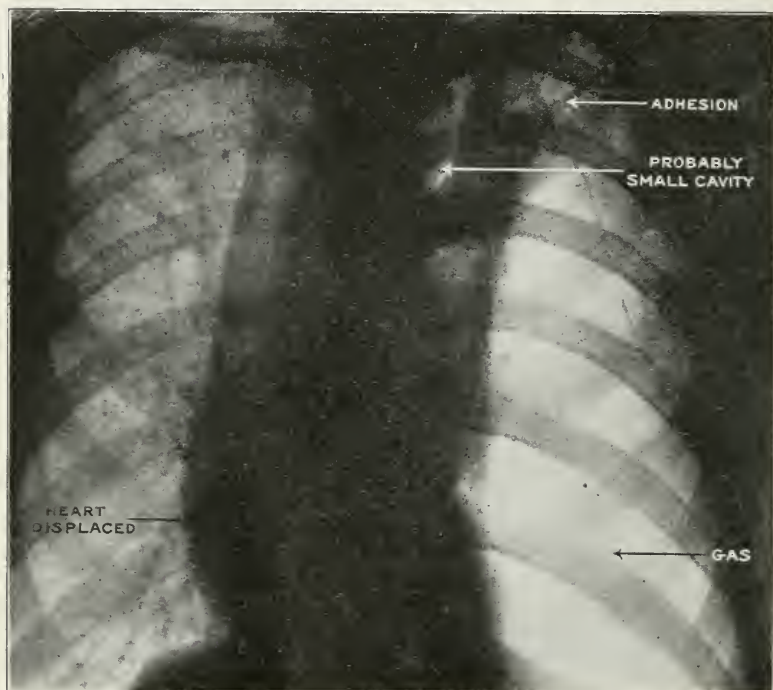
FIG. 2.—Successful left-sided collapse. (Mr. C., July, 1914.) Patient at work. Note marked mottling of sound side and displacement of heart to right of median line.

able to walk without fatigue for an hour or more daily, and were once more able to attend to their household duties or to resume work: in other words, they achieved an "economic recovery." Thus, 1 of these cases (Miss A., Fig. 1) collapsed in July, 1913, is living in the mountain region of Western Carolina attending to her household duties: 1, collapsed in 1914, has returned to teaching; 1, collapsed in 1914, returned to his work of collecting; 1, collapsed in 1914, resumed his studies in Florida; 1, collapsed in March, 1915, resumed her life in Indiana; 1, collapsed in 1914, has taken up the calling of a merchant in Asheville (Fig. 2); and 1 (Mrs. K., Fig. 3)

is still under my care doing very well indeed. These patients have not all stopped taking gas. I know that of the 7 cases 3 are still receiving injections, and perhaps a fourth, unless the effusion which developed on the collapsed side has wholly filled the pleural space. These 7 cases represent the actual saving of 7 lives, for in each case the results of prolonged rest in bed under a strict dietetic-hygienic regimen had born no results, and had it not been for the beneficial effect of collapsing the lung there would have been nothing left to do save to sit by and watch the patient die.
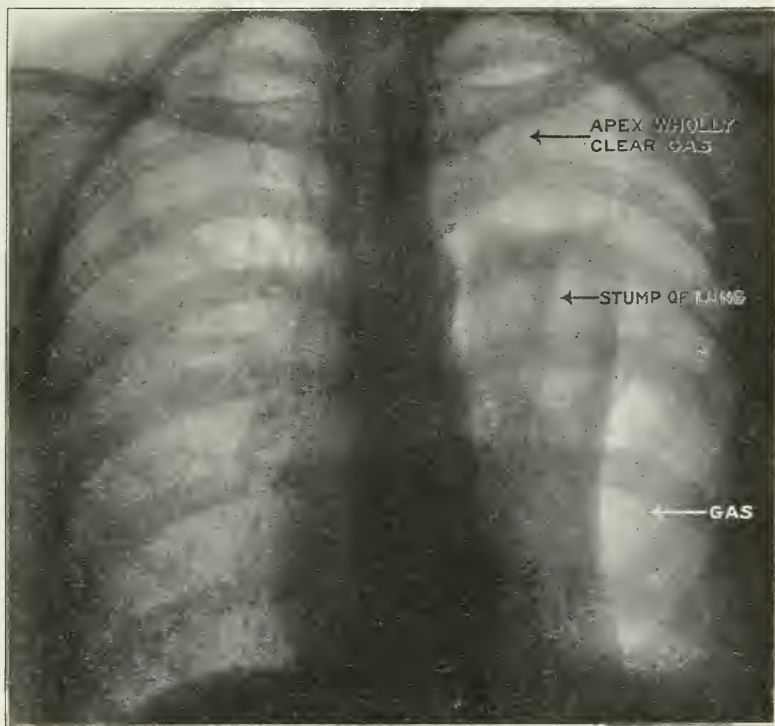
Fig. 3.—Successful left-sided collapse. (Mrs. K., January, 1916.) Lung compressed downward. No apical adhesions.

In my series 4 cases were compressed for the stopping of profuse and continued bleeding, and 3 out of the 4 were successes. In the fourth case the bleeding was stopped, but the patient was so nearly exsanguinated that he could not rally, and death ensued within three days. This case is, therefore, classified under the heading of Failure. The hemorrhage cases are not included under heading 1, because it was not my intention in these cases to continue compression after being certain beyond a reasonable doubt that a firm clot had formed over the site of bleeding. The procedure of compres-

sion was a temporary and an emergency measure. In one of these cases, that of a physician, I had declined to collapse his left lung a year previously because of too great involvement on the right side. I lost sight of him but was called in September, 1914, to find him bleeding profusely from the left lung.. Medical measures seemed to have no effect whatsoever. Gas was introduced on the left side and bleeding promptly stopped. The patient was well-nigh exsanguinated, but pulled through with the help of vigorous stimulation. Compression was maintained for two months. He then left, greatly improved, for his home in Virginia, and, I subsequently heard, became well enough to resume a limited amount of his practice. In another case seen in consultation the patient was so exsanguinated as to appear moribund; 3 injections of gas stopped the hemorrhage in this case, and bleeding never recurred. The patient eventually died of his tuberculosis, but lived on many months after the checking of the hemorrhage. Another case was given 3 injections within a week into the left pleural cavity for the purpose of controlling numerous moderate hemorrhages—3 or 4 ounces every four to six hours. Bleeding was checked by the first injection of 900 c c. of gas and wholly suppressed by the second injection of 600 c.c. given thirty-six hours later. The third injection of 600 c.c. was given four days later to ensue no further bleeding as the patient was not readily accessible, being some twenty miles from Asheville. His physician has recently written me that no further bleeding has occurred and that he has made uninterrupted improvement.

Though the number of cases in this class is small, yet the results have been so brilliant that I strongly advocate using gas for checking hemorrhage if severe or protracted, and influenced by medical measures.

I have 2 cases that I have grouped under heading 3: (Miss P., Fig. 3, and Mrs. W., Fig. 4). Both have been under observation for some time: 1 since December, 1914, and 1 since August, 1915. The lives of both have unquestionably been saved by pneumothorax, yet their condition now is by no means one approaching complete recovery. Temperature has been wholly banished in one case (Miss P.) and reduced to a maximum of 99.4° in the other (Mrs. W.), but cough and sputum containing tubercle bacilli continue to an amazing extent, though less so than before the use of gas. Both cases are moderately dyspneic and one (Miss P.) cannot do more than one-half hour's walking without distinct fatigue. Both are holding a rather subnormal weight, which, however, is rather characteristic of gas cases, due probably to a marked deficiency in the blood-oxygenating surface. The reason for the persistence of symptoms in the 2 patients is, as will be seen by consulting the roentgenographs, that an incomplete collapse has been obtained and one or more cavities are held open by pleural adhesions. The walls of the cavities being unable to coaptate, secretion continues,

hence cough and sputum. These patients have reached the limit of possible improvement as far as pneumothorax is concerned, and the gas injections should be continued indefinitely. This is not encouraging in one sense, and yet, on the other hand, there is no reason why both these patients should not enjoy their present state of health for years to come, and that state of health is such as to enable their lives to be by no means devoid of happiness and usefulness.
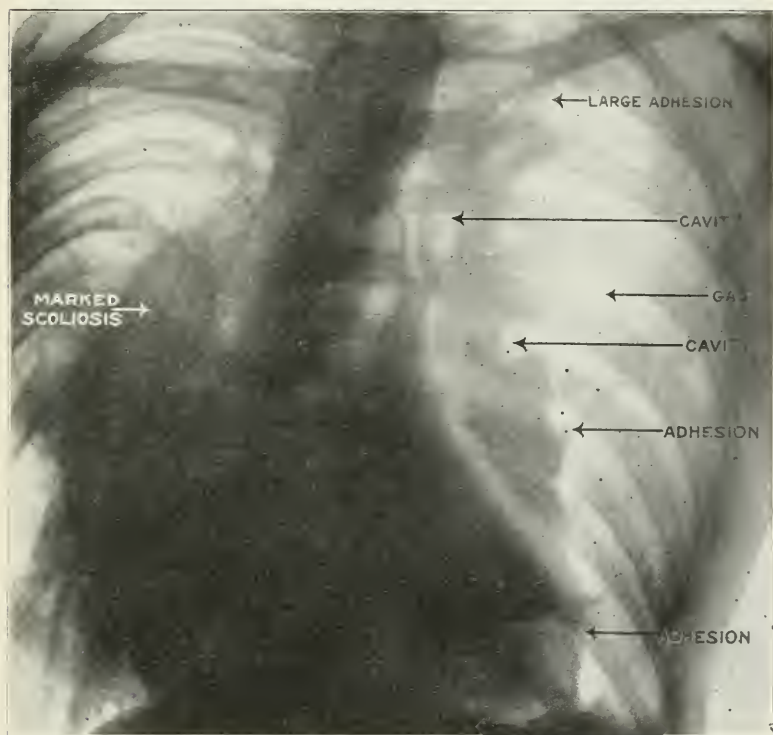

FIG. 4.—(Miss P., December, 1914.)   Left-sided collapse; partial success; gas still being continued.

Four cases appear under heading 4. All these patients have died, yet in all the gas alleviated their symptoms to a considerable degree, rendered them more comfortable, and appreciably prolonged their lives. In one case life was unquestionably prolonged for a year; in another for six months; in 2 others for at least four months. Death occurred in 1 case from a sudden dissemination of the tuberculous process in the uncompressed side, with symptoms typical of an acute suffocative phthisis; in 1 from an acute exacerbation of a chronic nephritis; in 1 from the development of a perforation from the pleural cavity into a bronchus with a resulting pyopneu-

mothorax; and in 1 from a gradual creeping spread of the tuberculous process in the uncollapsed lung; gas in these 4 cases was a palliative measure—a help—nothing more.

The last heading, that of Failure, looms large, embracing 14 cases, or 46.6 per cent. of the total number. The number is too great to permit of a detailed analysis of each case, but the following causes for non-success are assignable:
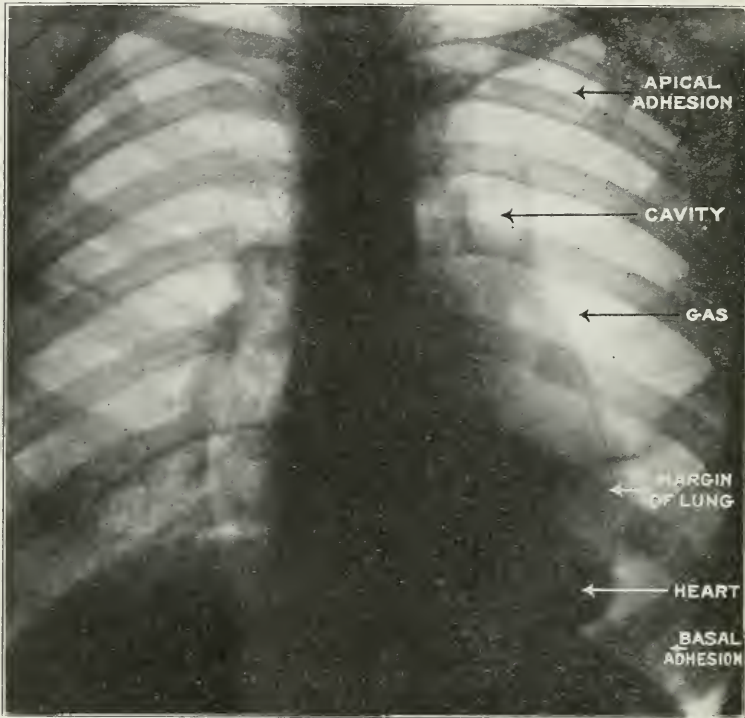
FIG. 5.—(Mrs. R., August, 1915.) Left-sided collapse; partial success; gas still being given.

1. Pocket formation: small amount of gas injected, but surrounding adhesions so dense as to preclude any appreciable amount of collape, 5 cases, or 35.7 per cent.

2. Adhesions so dense as to obliterate pleural space, 5 cases, or 35.7 per cent.

3. Compression obtained to a decided degree, but no result apparent, probably because of deep-seated undiscoverable or undiscovered disease in opposite side, 2 cases, or 14.2 per cent.

4. Development of tuberculous pneumonia in opposite side, 1 case, or 7.1 per cent.

5. Exhaustion: collapse obtained, but patient too near death to rally, 1 case, or 7.1 per cent.

It is thus readily seen that in over 71 per cent. of the failures adhesions were responsible. Adhesions are indeed the one great impediment to the successful beginning of a pneumothorax, and the one great obstacle to its becoming complete when started.

Upon looking over this brief review the conclusion is obvious that the method is worth while and that artificial pneumothax as a factor in pulmonary therapeutics has come to stay. Any method whatsoever that shows success in almost 25 per cent. of the cases cannot and should not be disregarded. In the hands of physicians experienced in lung work and having a full knowledge of the very simple technic and of the possible dangers, accidents due to this procedure should be reduced to a minimum, and many individuals otherwise hopelessly doomed should be restored to complete or comparative health and to many years of joy and usefulness.

A CONSIDERATION OF THE CAUSES OF RECURRENT SYMPTOMS AFTER OPERATION FOR GASTRIC AND DUODENAL ULCER.[1]

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(From the Surgical Service of Dr. A. A. Berg, Mount Sinai Hospital, New York.)

THE surgical treatment of ulcer of the stomach or duodenum does not terminate with the completion of the healing of the abdominal wound and the discharge of the patient from the hospital. It should properly be followed by a long period of careful after-treatment, extended over months and perhaps years, and directed toward the correction of those accompanying disturbances in the functions of the stomach which are always initiated by the ulcerative process. Such treatment is properly in the domain of the general practitioner from whom such patients are usually referred for operation, or in that of the expert medical man devoting himself to the care of these disorders of the stomach or duodenum. During this postoperative period symptoms frequently arise referable in a general way to the seat of the original trouble, at times at variance with those complained of before operation, at other times mimicking these ante-operative symptoms in some of their aspects, and often

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[1] Read at a meeting of the Medical Society of the County of New York. The subject here discussed was assigned by Dr. A. A. Berg, to whom I am indebted for this privilege, as part of a symposium on gastric and duodenal ulcer given from the service of Dr. Berg at Mount Sinai Hospital, New York.

again reproducing with faithful accuracy the original symptom-complex. Much against the usual impression prevalent among medical men these are not always due to the unhealed original lesion, or to its recurrence or to new ulcerations. Much oftener they are caused by other conditions which may be at a distance from the seat of the orignal trouble, or are due to disturbances of the normal physiology of the stomach or duodenum, or are consequent upon the new anatomical relations made at the operation.

For the purpose of pointing out the causes productive of these postoperative symptoms we have made a careful study of all of the patients operated upon for gastric or duodenal ulcer. We have correlated the postoperative complaints of these patients with anatomical and pathological facts made evident at secondary operations and have attempted to show the physiological relationships between the resultant postoperative symptoms and the causative objective findings.

It is essential that one have a clear conception of actual conditions at the time when these patients are discharged from the hospital. The ulceration is not the only condition which the patients have had. Associated lesions are always present which account for many of the symptoms. Anatomical changes in the wall of the stomach are produced by the inflammatory reaction around the ulcer. These lead to hypertrophy or rarely to atrophy of the mucous membrane, with immediate disturbances in the secretory function. Changes in the musculature lead to increased or diminished activity. Frequently mechanical faults in the emptying power of the stomach are added, having been initiated by stenoses of the pylorus or duodenum. The neighboring organs, too, are oftentimes compromised functionally by reflex disturbances and anatomically by adhesions or other abnormalities. Long periods of suffering have gradually brought about a curtailment in the amount of food taken and all of the patients come to operation in a more or less undernourished state.

The methods of surgical treatment which are employed on this service for ulcer of the stomach or duodenum depend naturally on the location of the ulcer and on the presence or absence of associated lesions. The methods are as follows:

1. The ulcer-bearing area is removed by local excision or by resection in continuity of the middle segment of the stomach.

2. The ulcer-bearing area is removed by pylorectomy or partial gastrectomy and a gastro-enterostomy is made.

3. A gastro-enterostomy is made and the ulcer-bearing area is excluded by the string method.

4. In a certain number, for technical reasons, the entire stomach and duodenum are excluded by making a jejunostomy. The patient is then fed through the jejunal tube.

The preparations for these operations, the operations themselves,

and any postoperative complications have all the more intensified the abnormal and undernourished condition present when the patient is first admitted to the hospital. Sufficient time after the operation has not elapsed, owing to the exigencies of hospital economy, for the readjustment to the normal of the accompanying disturbances in the physiology of digestion, and the associated gastritis has not had time to regress and disappear. However, the subjective symptoms have been alleviated and the gnawing pain and the distressing nausea and vomiting have disappeared. The patients believe that a cure has been accomplished and excesses are immediately committed and relatively enormous quantities of food, very often, too, badly prepared food, are taken. What is to be expected immediately happens and gives us the first and perhaps largest group of cases.

SYMPTOMS DUE TO FUNCTIONAL DISTURBANCES. These patients begin to complain immediately after their discharge from the hospital. The most common symptom is vomiting and very soon, if not corrected, pain appears, also pyrosis and gaseous eructations. Inquiry discloses the fact that food is being taken in too large quantities and the passage of the stomach tube reveals an abnormal residue of undigested and foul food detritus. Such a state of affairs was exemplified by one of our patients:

He was a man in the forties who had been operated upon for a perforated ulcer of the duodenum. A gastro-enterostomy had been made and the ulcer-bearing area had been excluded by the string method. Upon his discharge from the hospital he returned immediately to his ordinary diet, which was as follows: Breakfast: cereal, several eggs, several cups of coffee, and several rolls. Dinner: several eggs, fish, rolls, and coffee. Supper: soup, meat, potatoes and other vegetables and tea. It was to be expected that the man would complain. The distress which he had at first was soon augmented by nausea and relieved by frequent vomiting, symptoms which had not been present before operation.

This group of postoperative symptoms, which are the most commonly encountered because the patients are difficult to control after leaving the hospital, are easily relieved by a carefully arranged diet and a systematic course of stomach washings.

Ulcer of the stomach or duodenum is almost always associated with changes in the quality and relative quantities of the ingredients of the gastric juice. In the majority there is an hyperacidity, in the minority an hypoacidity, in a very few an anacidity. It is found that following the operation these changed conditions tend to adjust themselves and return to the normal. In the one case the amount of acid increases and in the other it diminishes. The hyperacidity present before operation may have been of an excessive degree, and it then frequently happens that the postoperative fall has not been sufficient to approximate to the normal and a state

of relative hyperacidity persists. Or it is found that the relative acidity having fallen to the normal level, returns after a short interval again to a hyperacid state. Hand-in-hand with this there is always associated a disturbance in the muscular activities of the stomach, leading to a delayed motility, so that abnormal residues are always found in the stomach.

This disturbed condition of the normal secretory function gives rise to symptoms that appear immediately or very shortly after operation. The great majority of these symptoms originate in indiscretions in diet; very few are due to a relative insufficiency in the size of the stoma. The usual symptoms are pyrosis and belching. Secondary symptoms due to a reflex interference with the motility of the large intestine lead commonly to various degrees of constipation, and in a few cases to diarrhea. With the gradual return of the normal strength of the patient and with ordinary judicious care these disturbances tend to right themselves. These cases form perhaps the second largest group.

The postoperative constipation may be a continuation of a similar condition which had preëxisted before operation and perhaps before the onset of the symptoms referable to the stomach or duodenum. Or it may represent an expression of a general atonic condition in which all of the abdominal viscera take part, produced by the handling of stomach and intestine during the operative procedures. It is difficult sometimes to distinguish between these two, and the test usually lies in the after-treatment. In the latter group the condition tends to improve quickly and spontaneously; in the former the condition is very stubborn and requires attention over a long period of time.

The diarrhea which may appear in a few patients is usually a new symptom and is due to changed physiological conditions in the stomach and small intestine, especially to the changes in the gastric and intestinal juices. It may be very mild and then is cause for little or no complaint. It may occur in periods separated by intervals in which the bowels act normally. In this group it is generally of moderate severity. In very rare instances the bowel evacuations are very profuse and are repeated with great frequency. The prognosis here becomes very grave, and almost always these cases go on to a fatal issue. There is no adequate treatment known for the grave form. In the other two groups the treatment must be directed toward the correction of the abnormally changed secretions of the stomach and small intestine and should be based on competent examinations of stomach contents and bowel evacuations.

Several other conditions giving rise to diarrhea after gastroenterostomy are pointed out by Mathieu and Savignac.[2] These are (1) gastrocolic fistula, (2) incomplete stenosis of the bowel,

2 Arch. d. Mal. de l'App. Dig., 1913, vii, 541.

and (3) jejunal ulcer. The first and second can usually be diag-
nosed by the roentgenograph; the third is discussed later in this
paper.

Other patients are found who frequently begin to complain even
before their discharge from the hospital. The symptoms described
are exactly the same which were present before the operation. In
contradistinction to the clinical course in the previous groups these
symptoms do not tend to right themselves nor do they improve
with the ordinary medical means. At varying periods afterward
secondary operations may be done, and then it is impossible to find
traces of any open ulcerations or of the scars of any healed ulcers, or
in fact any other intra-abdominal lesion amenable to surgical treat-
ment. It must be assumed therefore that in these patients there had
never been any lesion in the stomach and that the original operation
had been unnecessary. It may be stated as axiomatic that in order
to cure a patient of the symptoms of ulcer of the stomach an ulcer
must first of all be present.[3] [4]

SYMPTOMS DUE TO ANATOMICAL DISTURBANCES. Cases are also
found in which pain is experienced for a short time following opera-
tion. Usually after a period of medical treatment or sometimes
spontaneously improvement occurs and becomes permanent. These
symptoms are due to a want of accurate apposition in the suture
line of the gastro-enterostomy or remaining after the excision of the
ulcer-bearing area, with the development of a granulating area
which under proper conditions undergoes healing. In no sense
should these granulating areas be taken for the so-called peptic
ulcerations.

Perhaps more often than we have believed in the past, post-
operative symptoms may also be due to the cutting through of one
or more of the unabsorbable sutures which we are accustomed to
make use of in at least one of the rows of sutures in closing any
wound in the stomach or in uniting stomach to jejunum. The
symptoms then persist for a long time and would perhaps tend to a
spontaneous disappearance after the offending stitch had been cast
off, if it were not for the fact that both doctor and patient become
restless and a secondary operation is undertaken, which discloses a
piece of thread protruding from the suture line. In one of our
patients the same cutting through occurred with the exclusion
suture, and when the secondary pylorectomy was made half of the
string was found hanging free in a much narrowed pyloric lumen.

True peptic ulcerations appear in the line of the stoma or a short
distance therefrom in the jejunum in about 2 per cent. of those
patients who have a recurrence of their symptoms. The clinical
pictures are very characteristic and are as follows:

[3] Mayo, W. J.: Jour. Am. Med. Assn., 1915, lxiv, 2036.
[4] Moynihan: British Med. Jour., 1912, i, 347.

1. A reproduction of the original symptom-complex occurs within a short time after the operation and the patients believe that the old ulcer has reappeared. Progession may be very rapid and perforation with its consequent peritonitis may quickly arise.

2. The symptoms reappear within a short time after operation and continue much the same as before the operation. Most of the cases are in this second group. Sooner or later, too, most of these come to secondary operations.

3. The symptoms develop slowly and gradually a tumor forms in the upper abdomen. At operation one always finds that a fairly large jejunal ulcer has formed, has undergone subacute perforation, and has become surrounded by a large mass of indurated and adherent intestine and omentum. Such a condition is best treated by jejunostomy.

4. A tumor develops as in group 3. Suppuration occurs within it and the abcess ruptures into an adherent hollow viscus.

In other patients the period of good health extends over a much longer period than that indicated in all the previous groups, and the symptoms begin insidiously and increase slowly. With whatever other manifestation the clinical picture begins, vomiting soon appears and becomes prominent. Disturbances are found in the mechanics of the stomach, and these find their origin ususally in a progressive encroachment upon the lumen of the anastomotic stoma. Whenever the pyloric opening has undergone stenosis from some pathological lesion, or whenever the stomach has been unilaterally occluded, an abetting factor preëxists. We have no means except our own experiences in determining the final caliber of our stomata, and we are in the habit of providing for the expected contraction by making the openings overlarge. Nevertheless in a small percentage contraction occurs regardless of anything we may do. In a certain number, too, exuberant folds of mucous membrane falling across the opening of the stoma act as a valve and prevent the proper emptying of the stomach. Such valve formations sometimes occur much earlier. Occasionally, too, symptoms are produced by Murphy buttons when they do not cut through properly.

These symptoms may also be due to badly selected types of operations, such as some of the pyloroplasties, or to properly chosen but badly executed operations. The last are prolific in the production of kinks and other anatomical abnormalities or in the poor functioning of the anastomatic stoma.

At a secondary operation upon a patient who had developed symptoms some time after a gastro-enterostomy had been made for ulcer it was found that the lowermost part of the stoma had been obliterated by contraction. The opening remaining was very small and was situated rather high on the posterior stomach wall. This accounted for the symptoms and for the abnormal residues found in this patient's stomach.

SYMPTOMS DUE TO ANATOMICAL DISTURBANCES IN NEIGHBORING TISSUES. A certain number of the symptoms are due to other causes consequent upon our operations. Herniæ in the abdominal scars have often given rise to pain which closely simulates the pain of ulcer. Only when the herniæ are cured do the symptoms disappear. The literature describes several cases in which symptoms were due to chronic forms of ileus, of which the following are examples:

Moynihan.[5] In a patient with an ulcer of the stomach a suture gastro-enterostomy had been made. The postoperative vomiting persisted for one year after operation and then the abdomen was opened again. A hernia of the small intestine was found projecting into the lesser peritoneal cavity, the neck of the hernia being an opening in the transverse mesocolon adjacent to the stoma. The hernia was cured, the symptoms disappeared, and the patient remained well.

W. J. Mayo.[6] An anterior gastro-enterostomy was made with a Murphy button in a man for an ulcer of the pylorus and lesser curvature of the stomach. On the fourteenth day there were signs of intestinal obstruction which lasted for forty-eight hours. On the sixteenth day the button was passed, and thereafter the patient was discharged well. At the end of a year the patient returned, complaining of constant pain above the umbilicus. At the operation the jejunum was found twisted on its longitudinal axis and had passed behind the afferent loop. The old gastro-enterostomy was divided and a new retrocolic anastomosis was established. The final result is not given.

In a certain number of patients there seems to be a natural predilection toward the formation of postoperative intra-abdominal adhesions. These may be of moderate degree or may be very extensive. They occur also after operations upon the stomach or duodenum. Sometimes these adhesions result from the reparative peritonitis following localized inflammatory areas around the site of the operation, initiated by soiling during the procedures or by slight leakage thereafter. The resulting discomfort bears no relation, mathematically, to the extent of the adhesive peritonitis, but in a certain number the symptoms are apt to be referred to the stomach or duodenum. Sometimes in the course of time these symptoms disappear spontaneously. On the other hand, secondary operations may be found necessary either for persistent pain or vomiting or for acute or chronic obstructions.

Lesions in organs neighboring to or at a distance from the stomach or duodenum are occasionally found to give rise to symptoms which closely resemble those described before operation. The interval of good health may be several months or many years. This is

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[5] Duodenal Ulcer, London, 1912.   [6] Ann. Surg., 1902, xxxvi, 243.

especially apt to occur with lesions in the appendix and with chole-lithiasis. Moynihan describes such a case:

At the primary operation, which was for duodenal ulcer, stones were felt in the gall-bladder and for an unexplained reason these were left undisturbed. Following the operation the pain returned almost immediately and the abdomen was reopened again and a cholecystectomy was performed. The symptoms then disappeared. Such a history tends to question the validity of the original diagnosis.[7]

Other conditions which may give rise to symptoms referable to the stomach or duodenum are lesions in the spinal cord, especially tabes dorsalis and tumors. Patients are known to have been operated upon for gastric or duodenal ulcer who have later developed true gastric crises, the manifestations of which were referred for a time to the stomach and not to the spinal cord.

In the accompanying table it has been attempted to show statistically the pathological lesions which were found at secondary operations. The table includes cases from the literature and cases operated upon on Dr. Berg's service at Mount Sinai Hospital.

	Mount Sinai cases.	Cases from literature.
Contracted pyloroplasty	..	2
Contracted or closed stoma	5	3
Induration at stoma	2	
Murphy button	..	3
Peripyloric adhesions	1	1
Adhesions	..	3
Kink of afferent loop	..	1
Internal hernia	..	3
Healed ulcer	1	
No ulcer	2	2
Cholelithiasis	..	1
Suture ulcer	2	
Gastrojejunal ulcer	2	
Open ulcer and contracted stoma	1	
New ulcer	1	3
Open ulcer at old site	5	

The cases quoted from the literature are from case reports in the papers of Moynihan,[8] Munro,[9] W. J. Mayo[10], Noetzel.[11] Kocher,[12] Kelling,[13] Deaver,[14] Clairmont,[15] and Lieblein.[16] The tabel does not include the cases of gastro-jejunal ulcer described in the papers of Van Roojem[17] and Schwartz[18], nor those in the referate of Lublein.[19]

[7] Moynihan: Loc. cit.   [8] Med.-Chir. Trans., London, 1906, p. 471.
[9] Tr. Cong. Am. Phys. and Surg., 1907.   [10] Loc. cit.
[11] Deutsch. Chirurgen-Kongress, 1906, i, 87.   [12] Ibid., 1906, i, 80.
[13] Ibid., 1906, i, 78.   [14] Ann. Surg., Philadelphia, 1908, xlvii, 894.
[15] Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, xx, 330.
[16] Ibid., 1910, xxi, 842.   [17] Arch. f. klin. Chir., 1910, xci, 380.
[18] Ibid., 1914, civ, 694.
[19] Centralbl. f. d. Grenzgeb. d. Med. u. Chir., Ref., 1915, xix, 64.

Recurrent Ulcer. In discussing those postoperative symptoms due to a recurrence of the ulcerative lesions[20] only a few of the points will be mentioned. There are several factors to be considered:

1. The healing of the original ulcer.
2. The recurrence of the original ulcer.
3. The occurrence of new ulcerations.

It is not known which factor, preëxistent before operation, has been remedied or removed by any of the approved methods of operation. We simply know the crude fact that under proper postoperative medical care healing takes place afterward. What we are cognizant of are certain factors which are capable of delaying the healing of the ulcer. Clinically we know that tuberculosis and syphilis exert this delaying effect on all other diseased conditions, and especially on ulcerations on any of the body surfaces. Ulcers of the stomach and duodenum are no exceptions. The effect is produced most often by the toxic influences of a constitutional disturbance, or rarely it is due to local disturbance produced by the growth of tubercle or gumma within the confines of the ulcer. In the postoperative care of these patients these factors must all be reckoned with if a complete cure is to be expected.

Experimentally the work of Silberman,[21] Litthauer[22] and especially that of Creacimone and Anglesio[23] have shown that in animals the production of severe anemias is capable of prolonging the healing of defects much beyond the normal time. Many of our patients are anemic, quite a few profoundly anemic, and these experimental studies point out the necessity of correcting any such condition which may be present.

As regards the recurrence of the ulcerations or the formation of new ulcerations one may say very little for we are as little enlightened in this respect as in the etiology of the original ulcer. One point, however, should be brought out. A certain number are due primarily to infections with bacteria. The reliability of the work of Rosenow[24] and others showing that the portals of entry are frequently the teeth and the tonsils and that a selective localization of these bacteria occur in the stomach has not yet been firmly established. However, we have experiences described by Bolton[25] in which an exacerbation or a recurrence of symptoms had occurred in the course of a medical cure for gastric ulcer which followed a fresh attack of tonsillitis or an increase or reappearance of pyorrhea about the teeth. Many of our patients as we see them clinically,

[20] This subject was discussed in great detail by Dr. A. A. Berg at the symposium at which this paper was presented.
[21] Deutsch. med. Wchnschr., 1886, xxix, 497.
[22] Virchows Arch. f. path. Anat., 1909, cxcv, 317.
[23] Riforma Medica, Naples, 1914, xxx, 1289.
[24] Jour. Infect. Dis., 1915, xviii, 219; Jour. Am. Med. Assn., 1915, lxv, 1687.
[25] Ulcers of the Stomach, London, 1913.

exhibit a most deplorable condition of the teeth. Certainly in view of these experiences these conditions should be corrected.

A symptom-complex has been described by Eppinger and Hess[26] under the term vagotonia. Frequently these simulate accurately the picture of gastric or duodenal ulcer. It is quite within bound that the continued irritation of an old chronic ulcer may give rise to anatomical or functional disturbances of the vagi nerves. With the removal of the cause, however, one should expect that these disturbances would disappear.

In dealing with recurrent symptoms after operation for gastric or duodenal ulcer, all of these factors must be considered in correctly interpreting the clinical picture. Not always is it a matter of ease; frequently it is only decided at secondary operations which are always more or less in the nature of abdominal explorations.

A STUDY OF THE SIGNIFICANCE OF HEREDITY AND INFECTION IN DIABETES MELLITUS.[1]

By JOHN R. WILLIAMS, M.D.,

ROCHESTER, N. Y.

ALLEN, of the Rockefeller Institute, is of the opinion that diabetes is to be looked upon as a functional disturbance rather than as a disease in those organs which have to do with the metabolism of food. Clinical experience, in a measure, tends to support this view. So far as the writer has been able to learn, nomadic tribes and peoples living in a primitive state rarely if ever have diabetes; likewise other degenerative diseases, as arteriosclerosis, cancer, and disorders due to chemical and bacterial intoxications, are quite unknown. It would seem therefore that diabetes is a product of civilization. This phase of the problem, so far as the writer is aware, has never been carefully investigated. If such a thing were possible it would be interesting to study and plot mathematically all of the facts and forces which have played upon the body of the diabetic from the moment of his birth to the beginning of the disease and to correlate with these similar data with reference to his ancestors.

If it were possible to do this one might then be able to determine the influence of heredity, the various infections, chemical intoxications, etc., in the production of diabetes. To one or more of these agencies, at some time or other, has the cause of diabetes been ascribed. Making due allowance for inaccuracy of diagnosis

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[26] Ztschr. f. klin. Med. 1910, lxviii, 67.
[1] Oration in Medicine read before the Vermont State Medical Society.

in former years and for better methods of study now in use, one can scarcely fail to be impressed with the simultaneous increase in all degenerative diseases during the past thirty years. In the city of Rochester the comparative death rate from the most common diseases of degeneration is strikingly shown in the following tabulation:

DEATH-RATE PER 100,000 POPULATION.[2]

	1884.	1894.	1904.	1914.
Apoplexy	39.2	66.8	78.9	96.7
Cancer	49.9	24.3	80.5	108.5
Nephritis	55.8	62.1	101.6	107.7
Diabetes	2.9	7.4	16.2	17.1

These figures at least suggest that there is some factor common to these diseases.

The relation of heredity to diabetes has not been satisfactorily answered. In his recent book, Joslin[3] reviews the subject and concludes that heredity will appear more prominently in the case reports as time goes on, which he suggests may only reflect greater accuracy in vital statistics. He cites and confirms the experience of Naunyn that the more carefully he inquired into the family history the more commonly he found heredity to be present. This has been the writer's experience. Joslin thinks that the importance of heredity may be exaggerated by the fact that while diabetics are likely to know of diabetic relatives, non-diabetic patients give it little thought. He quotes the figures of Heiberg, who examined the family histories of 100 non-diabetics and found only 7 who had diabetic relatives, whereas 100 diabetics had eighteen relatives similarly affected. In 500 consecutive histories of non-diabetic patients, Joslin found only 25 relatives with the disease. It is questionable whether the problem can be fairly approached in this way. Many patients, both diabetic and non-diabetic, cannot account for the medical histories of their relatives. Furthermore, in the experience of the writer it is not enough to merely ask if any relative has had diabetes. The specific nature of the illness, the tenure of life, and the cause of death of each member of the family should be sought and only such histories accepted for study as afford a reasonable amount of data.

With this plan in mind the writer began about two years ago to gather information of this character and, from the records of several hundred individuals, he has selected the case histories of 100 diabetics for comparison with 100 non-diabetics. In but very few of these was it possible to get full data regarding all of the relatives, but none were used in which information regarding parents, grandparents, and brothers and sisters was not fairly complete and reliable. In this selection of cases completeness of data alone was considered. The occurrence of the most common degenerative diseases, arteriosclerosis, diabetes, cancer, and obesity,

[2] Data by George W. Goler, Health Officer, Rochester, N. Y.
[3] Joslin: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1916.

TABLE I.—SHOWING THE OCCURRENCE OF DIABETES, OBESITY, ARTERIOSCLEROSIS, AND CANCER IN THE PARENTS, GRANDPARENTS AND OTHER COLLATERAL RELATIVES OF 100 DIABETICS.

No. of patients	Diseases	Parents: Father	Parents: Mother	Grandparents: Paternal	Grandparents: Maternal	Collateral: Paternal	Collateral: Maternal	Familial	Children	Total occurrence
17	Diabetes only	1	3	1	2	3	9	7	1	27
31	Diabetes combined with arteriosclerosis, obesity, or cancer	3	7	1	7	7	16	13	4	58
Total 48		4	10	2	9	10	25	20	5	85
11	Arteriosclerosis only	6	3	1	2	4	3	0	0	19
30	Arteriosclerosis combined with diabetes, obesity, or cancer	10	6	8	7	13	2	7	0	53
Total 41		16	9	9	9	17	5	7	0	72
2	Cancer only	0	1	0	1	0	1	0	0	3
24	Cancer combined with diabetes, arteriosclerosis, or obesity	2	8	5	4	2	5	3	0	29
Total 26		2	9	5	5	2	6	3	0	32
Total 15	Obesity. Obesity combined with diabetes, arteriosclerosis, or cancer — All maternal relations in 9 cases; all paternal relations in 1 case.	0	3	1	2	3	0	5	0	32

Total cases with family histories free from diabetes, arteriosclerosis, obesity, etc. . . . 24

Total cases with family histories of diabetes, arteriosclerosis, obesity, etc. . . . 76

Total 100

were noted. It was assumed that if an individual before the age of seventy-five had a "stroke" or "sudden paralysis" or "dropsy" coming on after middle life in the absence of acute infection he had a sclerotic disease. This test was applied alike to both diabetic and non-diabetic groups. The data were so tabulated as to show differentially the occurrence of diabetes alone and in association with arterial disease, obesity, and cancer in the parents, paternal and maternal grandparents and collateral relatives (uncles and aunts and their children), and among the brothers and sisters (familial) and children of the patient.

These data in the case of the 100 diabetic patients are detailed in Table I, and for purposes of easy interpretation are summarized under the heading Summary of Table I.

SUMMARY OF TABLE I, SHOWING FAMILY HISTORIES OF 100 CASES OF DIABETES.

Cases in which no family histories of diabetes, arteriosclerosis, cancer, or obesity was obtained   24
Cases with family history of diabetes, arteriosclerosis, cancer, or obesity   76

Total   100
Seventy-six diabetic patients had:
85 diabetic relatives.
72 arteriosclerotic relatives.
25 obese relatives.
32 cancer relatives.
16 nerve, mental relatives.

Total   230

An examination of these tables shows most convincingly that diabetes, arterial disease, and obesity occur with extraordinary frequency in the parents and ancestors of diabetics, and also that they appear commonly in their progeny. That the phenomena observed in the diabetic group is unusual and not so characteristic of other groups of patients is shown by Table II and its summary, in which are exhibited data similarly gathered from 100 non-diabetic adults composed chiefly of individuals suffering from gastro-intestinal disturbances and a smaller number afflicted with cardiac, renal, and liver disease and minor disorders (Table II).

In the diabetic group, 48 patients had eighty-five either direct or collateral diabetic relatives, whereas in the non-diabetic group only 6 patients had eight diabetic relatives. In the diabetic group, six fathers and paternal grandparents and nineteen mothers and maternal grandparents had the disease. In the non-diabetic group only one father and maternal grandparent had diabetes. Indeed, the family histories of some non-diabetic cases strongly suggest that sooner or later they will become afflicted with the disease. Since diabetes is a disease which usually occurs well along in adult life, to minimize error only adult cases are considered in the non-diabetic group. Attention is directed to the preponderance of

TABLE II.—SHOWING THE OCCURRENCE OF DIABETES, ARTERIOSCLEROSIS, CANCER, AND OBESITY IN THE PARENTS, GRAND-PARENTS, AND OTHER COLLATERAL RELATIVES OF 100 ADULT PERSONS ILL FROM SOME OTHER CAUSE THAN DIABETES.

No. of patients.	Diseases.	Parents: Father.	Mother.	Grandparents: Paternal.	Maternal.	Collateral: Paternal.	Maternal.	Familial.	Children.	Total occurrence.
3	Diabetes only	1	0	0	0	0	2	1	0	4
3	Diabetes combined with arteriosclerosis, obesity, or cancer	0	1	0	1	1	0	1	0	4
Total 6		1	1	0	1	1	2	2	0	8
17	Arteriosclerosis only	5	2	4	8	4	3	4	0	30
21	Arteriosclerosis combined with diabetes, obesity, or cancer	5	5	3	3	2	7	1	0	26
Total 38		10	7	7	11	6	10	5	0	56
15	Cancer only	3	4	0	3	2	4	2	0	18
19	Cancer combined with arteriosclerosis, obesity, or diabetes	4	1	0	1	3	6	0	0	15
Total 34		7	5	0	4	5	10	2	0	33
2	Obesity only	2	1	0	0	1	2	2	0	8
4	Obesity combined with diabetes and arteriosclerosis	1	1	1	0	0	3	All maternal relatives obese in 2 cases.	0	8
Total 6		3	2	1	0	1	5	4	0	16

diabetic relatives on the maternal side, although it is quite generally
believed that the disease occurs more commonly in males than in
females. In the writer's series of 175 cases there were 96 males
and 79 females.

SUMMARY OF TABLE II, SHOWING FAMILY HISTORIES OF 100
CASES OF ILLNESS OTHER THAN DIABETES.

Cases in which no family history of diabetes, arteriosclerosis, cancer,
or obesity was obtained   47
Cases with family history of diabetes, arteriosclerosis, cancer, or
obesity   53
                                                          ———
    Total   100
Fifty-three non-diabetic patients had:

⎧ 6 diabetic relatives.
⎪ 38 arteriosclerotic relatives.
   34 cancer relatives.
⎪ 8 obese relatives.
⎩ 8 nerve, mental relatives.
                        ——
    Total   94

TABLE III.—48 CASES OUT OF 100 DIABETIC PATIENTS HAD
85 DIABETIC RELATIVES AS FOLLOWS:

Paternal.		Maternal.	
Fathers	4	Mothers	10
Grandparents	2	Grandparents	9
Collateral	10	Collateral	25
Total	16	Total	44
Brothers and sisters . .	20	Children	5

TABLE IV.—6 CASES OUT OF 100 NON-DIABETIC PATIENTS
HAD 8 DIABETIC RELATIVES AS FOLLOWS:

Paternal		Maternal.	
Fathers	1	Mothers	1
Grandparents	0	Grandparents	1
Collateral	1	Collateral	2
Total	2	Total	4
Brothers and sisters . .	2	Children	0

Equally interesting are the data regarding arterial disease. In
the diabetic group 41 cases had 72 arteriosclerotic relatives. In
the non-diabetic group 38 patients had fifty-six arteriosclerotic
relatives. Arteriosclerosis in the diabetic group preponderates on
the paternal side, occurring almost twice as often as on the maternal
side.

TABLE V.—41 CASES OUT OF 100 DIABETIC PATIENTS HAD
72 ARTERIOSCLEROTIC RELATIVES AS FOLLOWS:

Paternal		Maternal.	
Fathers	16	Mothers	9
Grandparents	9	Grandparents	9
Collateral	17	Collateral	5
Total	42	Total	23
Brothers and sisters . .	7	Children	0

TABLE VI.—38 CASES OUT OF 100 NON-DIABETIC PATIENTS
HAD 56 ARTERIOSCLEROTIC RELATIVES AS FOLLOWS:

Paternal		Maternal.	
Fathers	10	Mothers	7
Grandparents	7	Grandparents	11
Collateral	6	Collateral	10
	—		—
Total	23	Total	28
Brothers and sisters	5	Children	0

In the family history of diabetics it is not uncommon to find arteriosclerosis in the paternal line and diabetes and obesity on the maternal side. These are strikingly illustrated by the following case summaries:

CASE 1644.—Female; aged thirty-six years. Diabetes. Diabetes in four maternal generations.

Paternal.	Maternal.
Grandmother had arteriosclerosis	Grandmother had diabetes.
Father had arteriosclerosis	Mother had diabetes.
2 aunts had arteriosclerosis.	Aunt had diabetes.
2 uncles had arteriosclerosis.	

1 sister had diabetes.
1 brother had diabetes.
2 nephews had diabetes.

CASE 1660.—Male; aged thirteen years. Diabetes. Diabetes in four maternal generations.

Paternal.	Maternal.
Great-grandmother had cancer.	Great-grandmother had diabetes.
Father had arteriosclerosis.	Grandmother had diabetes and cancer.
	Mother had diabetes.
	Aunt had diabetes.
	Cousin had diabetes.

CASE 1717.—Female; aged forty-eight years. Diabetes and arteriosclerosis.

Paternal.	Maternal.
Father had arteriosclerosis.	Grandfather had arteriosclerosis
2 aunts had arteriosclerosis.	(relatives all short lived).

1 brother had diabetes.
1 brother had cancer.
1 sister had arteriosclerosis.
1 nephew had diabetes.
1 daughter had neurosis.

Similarly, obesity occurs more frequently in diabetic than in non-diabetic families, and maternal relatives are more often obese than are the paternal. Cancer occurs in one group about as often as in the other.

The most plausible explanation of the cause of diabetes is that advanced by Allen, namely, that the disease results from an exhaustion of the pancreatic cells. The facts here embodied are not

offered as proof that diabetes is inherited; they do justify the conclusion, however, that a favorable soil for the disease is created in the offspring of those afflicted either with diabetes or arteriosclerosis, or with both conbined, and to a lesser degree with obesity. Arteriosclerosis cannot be looked upon as a direct accountable factor because it is absent in diabetic children, although occurring frequently in their parents and grandparents. The very frequent association of diabetes and arteriosclerosis in middle-aged adults suggests a common cause and relationship, and that those agents which produce the one should be regarded as causal factors in the other. It is generally accepted that alcoholism, overeating, undue nerve strain, certain chemical, metabolic, and bacteriological intoxications, besides syphilis, may have etiological significance in the production of arterial degeneration. Of these deleterious agents infections must be seriously regarded. Arteriosclerotic individuals are very prone to infection, as are diabetics. So common are infections in these conditions that it is often quite difficult to say which is the more important or which antedates the other. Some workers in this field look upon diabetes as of bacterial origin. The frequency of occurrence of infection in the writer's series of cases is indicated in Table VII, in which are recorded only those infections which produce indubitable evidence of disease. Of these the most common are concealed infections in the teeth and tonsils.

TABLE VII.—A STUDY OF 100 DIABETIC PATIENTS, WITH REFERENCE TO ASSOCIATED SERIOUS INFECTION.

Infection.	No. of cases.
Teeth and gums	57
Teeth and tonsils	4
Tonsils	12
Appendix	6
Gall-bladder	4
Ear	1
Other infections	4
Syphilis	2
Cases with no evident infection	16
Cases with onset after injury	2

The true relation of infection to diabetes is not yet established. There are several possibilities, some of which are quite suggestive:

(a) It is possible that infection causes either the general arteriosclerosis which so commonly accompanies diabetes and thus leads to the premature involution of the individual; or

(b) A local sclerosis of the pancreas or other organs which have to do with food metabolism, according to Rosenow's elective affinity theory; or

(c) Acting as a fulminant it may precipitate a metabolic collapse by depressing the function of or otherwise incapacitating those organs of metabolism which may be inherently weak or have previously undergone sclerosis, also according to Rosenow's theory.

These opinions as to the relation of infection and sclerosis to diabetes, while largely conjectural, are in no small measure supported by clinical evidence and investigation. The following histories are submitted as cases in point:

CASE 1567.—Female; aged twenty years. Patient frail, delicate.

Family History. Father living at forty-five years; has diabetes. Mother died at thirty-eight years; cancer of uterus. One sister and one brother; both delicate. Maternal grandmother died at seventy-five years; arteriosclerosis and obesity. Weighed 268 pounds.

Patient for about three months had gastro-intestinal disease. When first seen on March 13, 1916, patient was suffering from an acute gastro-intestinal attack. Much pain and rigidity in right inguinal region. Nausea, vomiting, and constipation. Diagnosis of acute appendicitis made, which was confirmed by surgical counsel. History of intense thirst about two weeks previous. Former medical attendant claimed that urine before had always been sugar-free.

March 12, 1916. On general diet urine contained in fourteen-hour specimen 112 grams sugar, 2.6 grams ammonia. Patient presented evidence of impending coma.

March 14, 1916. Carbon dioxide tension of alveolar air 22.6 mm., Frederica apparatus. In a few weeks, symptoms of acute appendicitis subsided, acidosis disappeared, and food tolerance greatly increased. Then patient developed an acute tonsillitis and antrum infection which necessitated drainage operation. Coincident with this infection the food tolerance declined, acidosis developed, and the patient, while away from home, after an excessive indulgence in cake, candy, etc., died in coma. These data are graphically shown in accompanying chart.

It would seem that this patient inherited the liability to diabetes. Whether or not the acute appendicular inflammation precipitated the metabolic collapse, while suggestive, is not capable of proof, there is no doubt, however, of the influence of that infection and the succeeding ones destroying the tolerance of the patient and precipitating coma and death.

Another case is equally suggestive:

CASE 1517.—Female; aged seventeen years. Patient pale, slender, poorly developed.

Family History. Incomplete and indefinite. Mother delicate, prematurely old, and a neurotic.

September, 1914. Patient had inserted in upper jaw an elaborate bridge-work which necessitated the crowning of several teeth. One month later she began to gradually fail. Thirst, polyuria, and loss of weight and strength followed. Urine not examined until after the lapse of one year, when patient was referred to writer. At that time her teeth gave evidence of well-marked dento-alveolar disease. Tonsils hypertrophied, degenerated, and
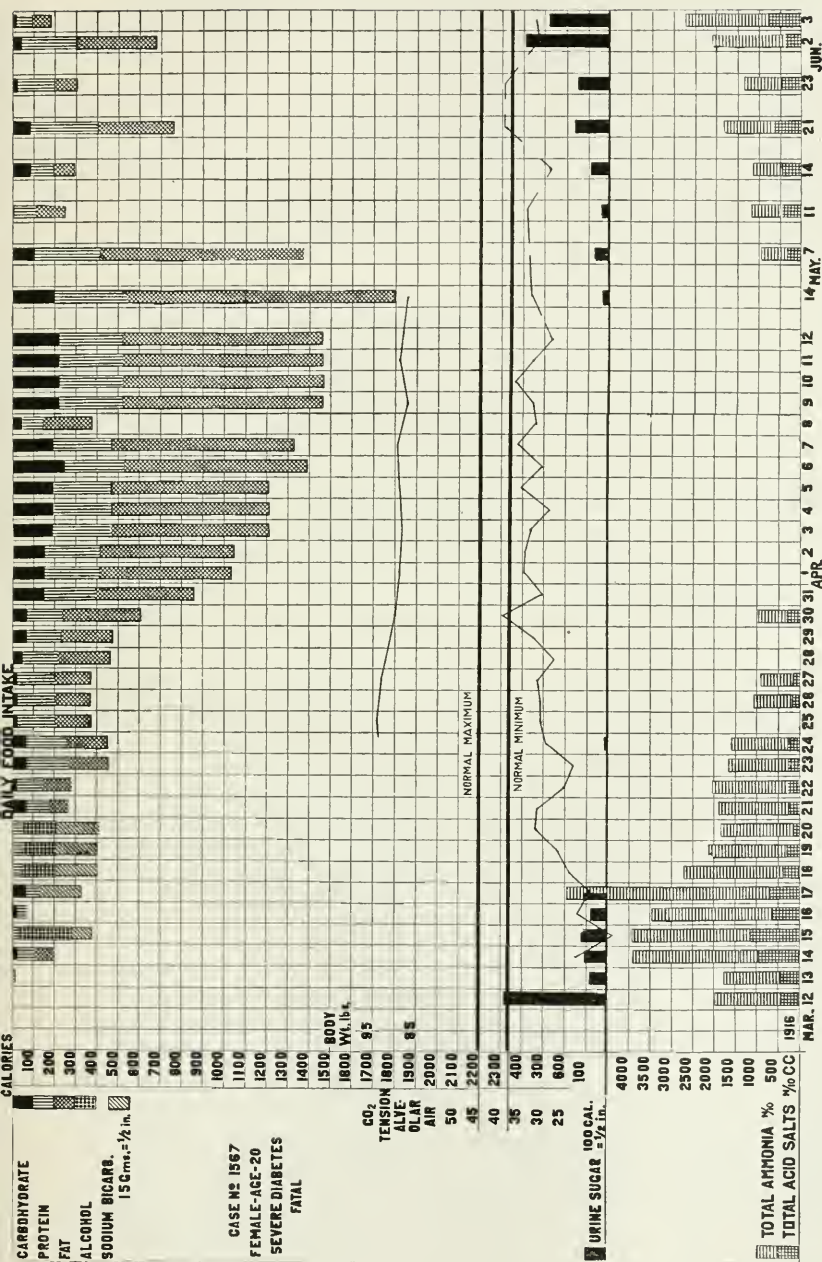
The data plotted hereon was designed to show the daily food intake and the effect of the diet as evidenced by the urine examination and lung air test. The food intake is plotted in calories, each food principle, including alcohol, having a different type of cross-hatching, as is indicated by the key. The total length of those several blocks represents the total caloric intake. Sodium bicarbonate is plotted in grams in which each subdivision, or one-half inch on the original chart, equals 15 grams. The carbon dioxide output of the lung air is plotted in millimeters of barometric tension. Urine sugar is plotted in calories on a base line so marked. Thus the carbohydrate intake can readily be compared with the carbohydrate loss or outgo. Urinary acid excretion is plotted in terms of decinormal alkali, as acid salts and ammonia, estimated by the Folin method. The sum of these is a fairly accurate expression of the total urinary acid excretion. From March 12 to March 24 the patient suffered severely from an acute attack of appendicitis. At the same time the patient exhibited a marked acidosis which gradually subsided as the gastro-intestinal disturbance disappeared. From April 1 to May 7 the diabetic condition improved materially; then the patient began to tonsillar, and antrum infection set in which destroyed her food tolerance, so that from then on, even though on a low diet, she was in a state of negative balance. This chart strikingly illustrates the influence of infection on metabolism

infected. Cervical lymph glands much enlarged, tongue swollen, and teeth marked. Patient in a state of advanced diabetes. Tonsils later enucleated, but parents objected to removal of insanitary bridge. Patient now has very little tolerance for food and remains in a state of low nutrition.

In this case the insertion of the bridge-work was immediately followed by dento-alveolar disease. Coincident with this came the diabetic symptoms. It is not unreasonable to assume that the impinging of this infection on a frail, poorly developed girl had something to do with the metabolic collapse which followed. These cases are not exceptional; they differ only in degree from many others which the writer might cite.

It is not the purpose of this paper to offer a new theory or to support or contest any of the older hypotheses as to the cause of diabetes but merely to emphasize to the clinician the importance of both arteriosclerosis and infection in diabetes. It would seem that the possible prevention or control of these factors would be a step in the direction of preventing the metabolic collapse which we call diabetes.

While the data herein submitted is insufficient and too limited to enable one to draw positive conclusions therefrom, it cannot be denied that it is extremely suggestive. In the mind of the writer it justifies the belief that:

1. The liability to arteriosclerosis and diabetes are transmissible from parent to offspring.

2. Infection, both acute and chronic, may precipitate a metabolic collapse or sufficiently lower the function of food metabolism in an individual with either general or local arteriosclerosis as to produce the clinical phenomena which we call diabetes.

3. Individuals with a family history of arteriosclerosis, diabetes, and obesity should be safeguarded against all latent and concealed or focal infections. Special attention should be directed to the head, so that dead teeth, apical abscesses, incompletely filled root canals, inflamed gums, infected and diseased tonsils, sinus and middle-ear disease should not exist.

4. Such individuals should be safeguarded in every way against those conditions which induce or hasten the arteriosclerotic process. Perhaps it is not going too far to say that individuals with an arteriosclerotic family history should not marry into diabetic families. Such a union is too frequently fraught with disaster to have it regarded with indifference. In the event of such marriage, until it can be proved otherwise, the children from this union should be carefully safeguarded along the lines indicated.

Medical literature affords little help as to how diabetes may be prevented. In view of the great and apparently increasing prevalence of the disease the writer has reported this limited investigation with the hope of stimulating further and more exhaustive inquiry in this direction.

A STUDY OF THERMIC FEVER, WITH SPECIAL REFERENCE TO THE BLOOD AND URINE CHEMICAL FINDINGS.

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AND

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Thermic fever is a term applied to certain symptom-complexes that are the result of disturbances of heat regulation, primarily from physical causes, the heat and water content of the air about the body, the condition of the peripheral vascular circulation, etc.; but these causes lead to chemical changes in the organism which are manifested in the characteristic clinical symptoms (auto-intoxication and retention) which, for a matter of classification, we would divide into two classes, namely, mild (due to overwork, bad ventilation, anxiety, worry, uncleanliness) and the severe (due to excesses, such as overeating and alcoholism). The causes of all are obviously the same. From a clinical stand-point we call those "mild" cases which reach a temperature of 107° or under and "severe" those which go above that point.

Taking the whole series of cases which may be included in the group, sunstroke and those due to heat prostration which occur in the absence of direct sunlight, we may state that insolation may occur under any circumstances in which heat accumulates in the body, and in which the body does not rid itself of its metabolic end-products such as urea, nitrogen, creatinin, and uric acid.

Hirsch[1] believed that while heat was the primary factor the immediate cause of the trouble was diminution of oxygen and retention of toxic principles. Vincent[2] also states his belief in a toxic basis. Gordon[3] says that recent work tends to the conception of paralyzing action on the nervous system of some toxic element which produces metabolic changes in the neurons, and according to the degree of auto-intoxication the effect of the sunstroke will be either an attack of ordinary heat-prostration or syncope, with unconsciousness or death.

If this be true, then insolation is an auto-intoxication brought about by substances formed in the body under abnormal conditions of heat retention as shown in our findings below. We wish in our figures on blood chemical changes to particularly emphasize the

[1] Quoted by Gordon: Osler, Modern Medicine, 1907, i, 52.
[2] Ibid.
[3] Osler: Modern Medicine, 1907, i, 52 (and R. G. Pearce, xxii, 525).

undue retention in these cases of the non-nitrogenous constituents of proteid metabolism.

The following cases occurred in the service of one of us (Schisler) in the St. Louis City Hospital.

CLINICAL HISTORIES AND LABORATORY DATA.

Evans: male; aged fifty years; brewery worker; habits irregular; entered 5.30 p.m. August 5, 1916; unconscious; temperature, 110.4° (rectal); pulse, 130; respiration, 36; pupils contracted, reaction to light negative; general spasticity of body present; knee-jerks increased; toe signs questionable. The average blood-pressure taken during observation was systolic 91, diastolic 46 (Tycos); 30 c.c. spinal fluid (under normal pressure) was negative (Wassermann); urine albumin $+++$; many granular and pus casts. The man developed several generalized convulsions; pulse gradually became weaker; died August 6. No autopsy.

Summary. The question of uremia was thought of; this was ruled out because of the low blood-pressure. Cerebrospinal lues was questionable, the spinal fluid being negative. Diagnosis: thermic fever. No blood data on this case.

Muich: male; aged forty-five years; laborer; habits irregular; entered 4.45 p.m. July 30, 1916; unconscious; temperature, 108.6° (rectal); pulse, 110; irregular respiration, 48; pupils reacting to light; no rigidity or convulsions; heart irregular, with no positive findings; reflexes sluggish; stool and urine involuntary; emesis greenish-colored fluid; blood-pressure (systolic), 100; developed alcoholic psychosis and marked hallucinations; became rational four days after entering, when he gave a history of previous attack of thermic fever. Recovered, leaving hospital August 6, 1916.

August 4. Urine, no data.

Blood: Urea nitrogen, 19 mgm. per 100 c.c.; uric acid, 3.3 mgm. per 100 c.c.; creatinin, 3 mgm. per 100 c.c.; sugar, 0.138 per cent.

Summary. Observation made when convalescent; retention not great. It will be noted that this case while it displayed severe clinical symptoms did not show in its blood chemistry any cause for making a fatal prognosis. His urea nitrogen was 19, uric acid 3.3, creatinin 3 mgm., blood-sugar, 0.138 per cent.; values slightly above normal. It must be remembered that his urinary findings were the same as those of the cases that died and the other cases that recovered, namely, albumin and casts.

Ship: white; male; aged fifty-three years; bartender; habits irregular; entered 6.15 p.m. July 31, 1916; unconscious; temperature 108.2° (rectal); pulse, 180; irregular; respiration 40, labored; systolic murmur of apex; contraction of heart poor; pupils contracted, reaction to light sluggish but equal; regained consciousness on the second day but remained irrational. Developed alcoholic

psychosis; on the fourth day a secondary rise in temperature of 104.2° (axilla) and generalized convulsions; died August 4, 1916. No autopsy. Note the marked retention in the laboratory report below:

August 3. Urine: Albumin, very faint trace; sugar, negative; acetone, negative; diacetic acid, negative; indican, moderate amount.

Blood: Urea nitrogen, 76 mgm. per 100 c.c.; uric acid, 14.8 mgm. per 100 c.c.; creatinin, 6.1 mgm. per 100 c.c.; sugar, 0.177 per cent.

Summary. Moderate number of epithelial cells and leukocytes; very occasional red blood cells; two finely granular casts found after a prolonged search; clinical signs good; retention high, attracting attention to fatal prognosis. Died one day later.

It was noted in this case that his original symptomatology did not attract our attention to any fatal ending. On the contrary he seemed in rather good shape. He entered on July 31. On August 3 his blood findings showed high retention, the most significant observation in the same being the creatinin value of 6.1 mgm. This observation was made from blood obtained in the morning. On the following morning he died.

Huth: white; male; aged forty-two; concrete worker; habits irregular; entered 6.15 P.M. July 29, 1916; unconscious; temperature, 108.2°; pulse, 170, regular; respiration, 36; generalized convulsions; labored breathing; pupils contracted; reaction sluggish; knee-jerks increased; toe signs questionable; developed second rise in temperature and alcoholic psychosis; regained consciousness the fourth day. Average blood-pressure, 120. Discharged, well, August 26, 1916.

August 2. Urine: Albumin, moderate amount; sugar, negative; acetone, small amount; diacetic acid, small amount; indican, moderate amount.

Blood: Urea nitrogen, 26 mgm. per 100 c.c.; uric acid, 9.6 mgm. per 100 c.c.; creatinin, 3.83 mgm. per 100 c.c.; sugar, 0.168 per cent.

August 12. Urine: Albumin, negative; sugar, negative; acetone, negative; diacetic acid, negative; indican, negative.

Blood: Urea nitrogen, 14 mgm, per 100 c.c.; uric acid, 3.3 mgm. per 100 c.c.; creatinin, 2 mgm. per 100 c.c.; sugar, 0.12 per cent.

Summary. Moderate number of coarsely and finely granular casts and occasional leukocytes; very occasional leukocyte. Retention not high; patient recovered, although clinical signs seemed bad. This is an interesting case in that his symptoms were very severe, and yet blood chemical findings at this time did not indicate much retention, an observation which was well borne out by later tests and the ultimate fate of this case. On the tenth day of his stay in the hospital his blood findings were practically normal and his recovery certain. He was discharged on the twenty-eighth day of his stay.

O'Connor: white; male; brewery worker; habits irregular; married; entered 4.40 P.M. July 31, 1916; unconscious; temperature, 110.5°; pulse, 160, thready in character; respiration, 44, labored; heart action very weak; pupils markedly contracted, no reaction; generalized convulsions, with marked spasticity; did not regain consciousness; lumbar puncture made and 35 c.c. of clear fluid under normal pressure was obtained; became progressively worse; died 8.20 P.M. August 1, 1916.

August 1. Urine: Specific gravity, 1015; albumin, moderate amount; sugar, negative; acetone, negative; diacetic acid, negative; indican, very large amount. Serious findings.

Blood: Urea nitrogen, 33 mgm. per 100 c.c.; uric acid, 1.32 mgm. per 100 c.c.; creatinin, 4.8 mgm. per 100 c.c.; sugar, 1.5 per cent.

Summary. Moderate number of coarsely granular casts and red blood cells; occasional leukocytes. Retention high; patient died same day. We might call attention to our observations above on Ship case as applying in all particulars to this case.

Fischer: white; male; aged forty years; plumber; married; habits irregular; entered 8.50 P.M. July 30, 1916; unconscious; temperature, 109° (rectal); pulse, 150, regular but weak; respiration, 30; breathing irregular and labored; pupils dilated, reaction very sluggish; knee-jerks sluggish; toe signs questionable; general spasticity of body present; became conscious on third day but irrational; developed convulsions of a generalized type. The blood-pressure taken at intervals was systolic, 109, diastolic, 87 mm. The white blood count was 10,000; Wassermann blood and spinal fluid negative.

August 2. Urine: Albumin, very large amount; sugar, negative; acetone, moderate amount; diacetic acid, moderate amount; indican, moderate amount.

August 8. Urine: Albumin, negative; sugar, negative; acetone, negative; diacetic acid, negative; indican, trace.

August 12. Urine: Albumin, negative; sugar, negative; acetone, negative; diacetic acid, negative; indican, very large amount.

August 2. Blood: Urea nitrogen, 32 mgm. per 100 c.c.; uric acid, 8.6 mgm. per 100 c.c.; creatinin, 4.1 mgm. per 100 c.c.; sugar, 0.162 per cent.

August 3. Blood: Urea nitrogen, 39 mgm. per 100 c.c.; uric acid, 9.8 mgm. per 100 c.c.; creatinin, 4.56 mgm. per 100 c.c.; sugar, 0.165 per cent.

August 4. Blood: Urea nitrogen, 39 mgm. per 100 c.c.; uric acid, 7.9 mgm. per 100 c.c.; creatinin, 4.47 mgm. per 100 c.c.; sugar, 0.18 per cent.

August 8. Blood: Urea nitrogen, 45 mgm. per 100 c.c.; uric acid, 7.1 mgm. per 100 c.c.; creatinin, 3.94 mgm. per 100 c.c.; sugar, 0.156 per cent.

August 8. Spinal fluid: Urea nitrogen, 44 mgm. per 100 c.c.; uric

acid, 0.88 mgm. per 100 c.c.; creatinin, 2.4 mgm. per 100 c.c.; sugar, 0.1 per cent.

August 10. Blood: Urea nitrogen, 55 mgm. per 100 c.c.; uric acid, 6.9 mgm. per 100 c.c.; creatinin, 5 mgm. per 100 c.c.; sugar, 0.174 per cent.

August 12. Blood: Urea nitrogen, 89 mgm. per 100 c.c.; uric acid, 8.2 mgm. per 100 c.c.; creatinin, 5 mgm. per 100 c.c.; sugar, 0.2 per cent.

Summary. Urinary findings indicated some marked renal disturbance, but not of the same importance as blood findings. Remarkable number of casts on last day of life. High retention, indicating probable fatal outcome. Patient died two days after creatinin reached 5 mgm. per 100 c.c. This was the most interesting case of our series, because it showed the typical high retention, gradually increasing, of all the constituents, finally reaching the fatal "creatinin" point of 5 mgm. Again, this patient lived fourteen days in practically an unconscious state, finally dying with the findings at autopsy above catalogued. It is also to be noted that the macroscopic and microscopic findings, particularly of the kidneys, showed nothing chronic, simply a cloudy swelling and possible passive congestion. This, of course, rules out the possibility of the blood retention in this case, being due to any pre-existing renal deficiency.

Postmortem examination of this case was made by Dr. D. F. Hochdoerfer, whose courtesy in demonstrating the gross changes we wish to acknowledge.

The complete autopsy report follows:

Color, white; sex, male; height, 5 feet 8 inches; weight, 130 pounds; hair, blond; eyes, gray.

External appearance: No evidence of external violence. Body emaciated.

Rigor mortis: Present.

Scalp: Normal.

Skull: Normal.

Membranes of brain: Thickened and adherent.

Brain: Watery and anemic.

Spine and spinal cord: Spine normal. Spinal cord at cervical section normal.

Pleural cavities: Adhesions right cavity.

Lungs: Pneumonic areas in right lower lobe. Bronchi filled with bloody, watery secretion. Right lung on section contained a large amount of watery exudate. All evidence of a bronchopneumonia present.

Intestines: Normal.

Liver: Fatty.

Spleen: Small.

Pancreas: Normal.

Kidneys: Parenchymatous and interstitial changes present. Cloudy swelling. Capsule slightly adherent.

Bladder: Normal.

Male genitalia: Normal.

Remarks: History, insolation July 30, with temperature 107°.

Pieces of the various organs were taken for microscopic examination, namely, brain, heart, spleen, pancreas, liver, and kidneys. The most definite changes were seen in the kidney structure. Here we had a typical picture of cloudy swelling without any of the well-marked changes of a preëxisting or long-standing degeneration.

The gross and microscopic changes in this case indicate a simple passive congestion of the kidneys and the usual absence of gross or minute manifestations as commonly seen in thermic fever.

We give below a summary of the blood and urinary findings in these cases.

CASE	DATE 1916	OUTCOME	UREA NITROGEN (MGMS. PER 100 cc)	URIC ACID	CREATININE	SUGAR (PER CENT)	REMARKS	SPECIFIC GRAVITY	ALBUMIN	SUGAR	ACETONE	DIACETIC ACID	INDICAN	MICROSCOPICAL EXAMINATION	REMARKS
BLOOD ANALYSIS								**URINE ANALYSIS★**							
O'Conner	8/1	DIED	33	132	4.80	150	RETENTION HIGH PATIENT DIED SAME DAY.	1015	#	Neg	Neg	Neg	###	Moderate number of coarsely granular casts and red blood cells. Occasional leucocytes.	FINDINGS SERIOUS
Fischer	8/2		32	86	4.1	0.162	High retention indicating probable fatal outcome. Patient died two days after creatinine reached 5.0 mgms. per 100 cc		###	Neg	#	#	#	Moderate number of granular casts and epithelial cells.	Urinary findings indicated some marked renal disturbance, but not same importance as blood findings.
	8/3	DIED	39	98	456	0.165									
	8/4		39	79	447	0.180									
	8/8		45	71	3.94	0.156			Neg	Neg	Neg	Neg	Trace	Moderate number of epithelial cells leucocytes and finely granular casts.	
	8/9		44	0.88	2.4	0.10									
	8/10		55	69	5.0	0.14									
	8/12		89	8.2	5.0	0.20			Neg	Neg	Neg	Neg	###	Very many granular casts and occasional leucocytes. Such number of casts is rarely seen.	Remarkable number of casts on last day of life.
Huth	8/2	RECOVERED	26	96	383	0.168	Retention not high. Patient recovered although clinical signs seemed bad.		#	Neg	+	+	#	Moderate number of coarsely and finely granular casts and occasional leucocytes. Very occasional leucocyte.	
	8/12		14	33	2.0	0.120			Neg	Neg	Neg	Neg	Neg		
Ship	8/3	DIED	76	148	61	0.177	Clinical signs good. Retention high, attaching attention to fatal prognosis. Died one day later.		Very faint Trace	Neg	Neg	Neg	#	Moderate number of epithelial cells and leucocytes. Very occasional red blood cells. Two finely granular casts found after a prolonged search.	
Muich	8/4	RECOVERED	19	33	30	0.88	Observation made when convalescent.								

★ ### Very large amount
Moderate amount
+ Small amount

Fig. 1

For purposes of comparison we give a charted description of the blood changes in some of the well-known conditions in which the microchemical methods of Folin, Denis, Benedict, Lewis, Myers, and Fine have been worked out.

In passing it might be added that the blood-chemical analyses were made following the technic that has been elaborated by Folin and others. The blood was uniformly taken in the morning before nourishment was given. It was procured from one of the superficial veins on the forearm, received into potassium oxalate and defibrinated. A portion was precipitated at once with picric acid

for sugar and creatinin estimations, the balance being used for the urea-nitrogen and uric-acid determinations. For the sugar estimations we used the method of Benedict and Lewis;[4] for the creatinin, the method of Folin;[5] for the urea, the urease method of Marshall[6] and Van Slyke;[7] for the uric acid, the method of Folin[8] modified by Benedict.[9] In all cases we used the Hellige instrument in making our determinations.

THE CHARACTERISTIC BLOOD PICTURES IN GOUT, DIABETES & NEPHRITIS II	UREA N, URIC ACID, CREATININE & SUGAR.			
DISEASE	**UREA N**	**URIC ACID**	**CREATININE**	**SUGAR**
	MGMS. PER 100cc of BLOOD			PER CENT
NORMAL	12-15	1-3	1-2.5	0.08-0.12
GOUT		3.5-6		
MILD DIABETES				0.15-0.30
SEVERE DIABETES				0.30-1.10
CHRONIC NEPHRITIS	15-50	1-4	1-3	
UREMIC NEPHRITIS	80-300	4-15	4-34	0.10-0.20
THERMIC FEVER	UREA N 26-89	URIC ACID 6-14	CREATININE 3-6.1	SUGAR 0.15-0.20

Fig. 2

CONCLUSIONS. The study of these cases from the laboratory stand-point has been most instructive. Here we have in thermic fever a condition that is unquestionably analogous in its symptomatology to some form of uremia. Again, we have in the urinary findings a close resemblance to this condition. We found in the blood-chemical analyses of these cases high retention of the nonprotein nitrogen constituents, indicating clearly a deficiency of renal function. In some cases the retention was high and the symptomatology not bad, yet these cases died. In other cases we found low retention and bad symptoms, and the patients uniformly recovered. Is this not then a truer guide to the exact status of the patient from the stand-point of prognosis than the data obtainable either from the clinic or urinary analysis? We do not wish by any means to insinuate that the whole course of any

[4] Jour. Biol. Chem., 1915, xx, 61.
[5] Am. Jour. Physiol., 1905, xiii, 45.
[6] Jour. Biol. Chem., 1913, xv, 487.
[7] Ibid., 1914, xix, 211.
[8] Proc. Am. Soc. Biol. Chem., 1915.
[9] Jour. Biol. Chem., 1915, xx, 629.

case can be completely predicated upon the blood-chemical findings, but we do insist upon the great value of this work in this and allied conditions. The determination of the amount of creatinin in these cases has given us some figures which seem to bear out the contention of Myers and Lough[10] that a percentage of creatinin that exceeds 5 mgm. per 100 c.c. of blood bodes ill for the patient. It will be noted that in the cases of O'Connor, Fischer, and Ship we had a creatinin value around or above 5 mgm. These three cases died. In the case of Ship at the time his blood was taken his clinical condition did not seem to be nearly as bad as that of Huth, yet the creatinin value of the former was above the so-called fatal point, whereas the latter had only a creatinin retention of 3.83 mgm. The of case Ship, however, vindicated the prognostic value of a high creatinin retention, as he died on the morning following this determination, yet Huth, whose blood-creatinin was 3.83 at the time that his clinical condition seemed to point to a fatal ending, recovered, showing ten days later practically normal blood figures. Thermic fever can be added therefore to the set of conditions which with high creatinin value, 5 mgm. or over, can be said to offer a fatal prognosis. For all intents and purposes these figures in thermic fever may be construed as similar in their interpretation to those obtained in severe uremic nephritis.

TREATMENT. A word or two in regard to the treatment of these cases: tub baths, gradually cooling the water to ice bath until the patient's temperature was reduced to 104° or under; stimulation with camphor, strychnin, and digitalin, free elimination, proctoclysis, with normal saline solution. In general, symptomatic treatment.

We wish to extend our thanks to Mr. A. J. Blaivas for valuable assistance in the chemical analyses and to Drs. Irvin Schmidt and W. I. Smith, of the staff of the hospital, for their active coöperation.

THE CLASSIFICATION OF THE CHRONIC HIGH BLOOD-PRESSURE CASES.

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THERE is no subject in medicine which, in the present age, has more vital interest to physicians than that of the chronic diseases of the circulatory system. Figures in all vital statistics have shown us that all affections of the circulatory and renal systems are definitely on the increase. "Arterial diseases of various kinds,

[10] Arch. Int. Med., 1915, xvi, 536–546.

atheroma, aneurysm, etc., caused 15,685 deaths in 1915, or 23.3 per 100,000. This rate, although somewhat lower than the corresponding ones for 1912 and 1913, is higher than that for 1914, and is very much higher than that for 1900, which was 6.1."[1] True, the average length of life has been considerably prolonged in the past twenty-five years, yet it is not due to a decrease in the incidence of these chronic diseases. We are not absolutely certain yet of the causes which are concerned in the increase of the chronic affections of the circulatory and renal systems, but our modern life, with its stress and strain, its mental concentration and overindulgence in protein food, must have some large part in the production of these diseases.

The study of the cardiovascular system has been greatly advanced by the introduction of instruments of precision which measure the blood-pressure, record the radial pulse, the venous pulse, the venous pressure, and record on photographic paper or film the electrical variations of the parts of the heart. Again, the introduction of various tests to measure the functional capacity of the kidneys has added immensely to our knowledge of various kidney diseases, and has been of great help in prognosis. To keep pace with the advances in these closely allied branches of medicine taxes the time and energy of any man. All that we can hope to do is to gather together a few of the generalizations and apply them as best we can to our daily work.

Blood-pressure as an aid to diagnosis has been badly used and much abused. Some have even expected the instrument to name the diagnosis, and when it, unlike Balaam's ass, was silent the instrument was blamed and discarded as worthless. Such an attitude is puerile. It is largely the result of taking only systolic pressure and neglecting the important diastolic and pulse-pressure. Happily this conception of blood-pressure is now undergoing a change, and we confidently expect to find that much help in diagnosis and prognosis will be given by careful blood-pressure estimations.

Five so-called phases have been described in the auscultatory blood-pressure phenomenon.[2] The systolic pressure is read at the beginning of the first phase and the diastolic, as I have shown,[3] is read at the sudden transition from the third to the fourth phase, or where the loud third sound suddenly becomes dulled. From there to the fifth phase, that is, no sound, is usually only from 4 to 6 mm. For those who find difficulty in determining the sudden transition of sound the fifth phase may be used. Hooker and Southworth[4] conclude from their observations that for clinical purposes the diastolic pressure may be taken at the disappearance of

[1] United States Mortality Statistics for 1915.
[2] Korotkov: Mitt. d. k. mil. med. Akad. zu St. Petersburg, 1905, xi, 365.
[3] Warfield, L. M.: Arch. Int. Med., 1912, x, 258.
[4] Arch. Int. Med., 1914, xiii, 384.

all sounds (the fifth phase). I have called attention, however, to the fact that in cases of aortic insufficiency there is no fifth phase, that is, the fourth phase or dull tone is heard over the uncompressed artery, hence one could not use the point of disappearance of sound to determine diastolic pressure. Must one then conclude that there is no diastolic pressure in aortic insufficiency? That would be absurd. One can easily obtain the diastolic pressure by taking the sudden transition of third into fourth phase. As a matter of fact, except in cases of aortic insufficiency, one may use the fifth phase to determine the diastolic pressure. It must, however, be remembered that there is an error of 4 to 6 mm. normally and up to 16 mm. in high-pressure cases.[5]

In an irregular heart, especially in the cases due to myocardial disease, it is quite impossible to determine the true diastolic pressure. One can only approximate it and say that the pulse-pressure is low or high. As a matter of fact the real systolic pressure cannot be determined. For this figure the place on the scale where most of the beats are heard may be taken for the average systolic pressure. No one can seriously maintain that he can measure the diastolic pressure under all circumstances.

By means of the auscultatory method of measuring blood-pressure we are able to determine irregularities of force in the heart beats more easily than by listening to the heart sounds. A pulsus alternans is readily made out. The irregular tones heard over the brachial artery in cases of irregular heart action have been called "tonal arrhythmias."[6]

There are three parts to every blood-pressure estimation: the systolic, the diastolic, and the pulse-pressure. These I have called the pressure picture.[7] To these should be added the pulse-rate in order to make the reading complete. Obviously, to say that the systolic pressure is 140, 160, or 200 mm. Hg. conveys to more knowledge of what the heart is doing than a count of red cells alone determines the kind of anemia. We have long known that a great variety of influences modifies the systolic pressure. Some of the influences are psychic and are entirely beyond our or the patient's control. Some apparently trivial circumstances, a chance remark made to the patient, an occurrence earlier in the day the memory of which flashed through his mind, may and does increase the systolic pressure 20 mm. or more above the average normal for the person. The systolic pressure measures the total work of the heart at the moment when it is tested. In a few minutes it may be higher or lower. A pathological or, rather, a compensatory high systolic pressure is always high, but the height is subject to great variation which makes it unwise to attribute a drop in pressure to any therapeutic measure.

5 Warfield, L. M.: Jour. Am. Med. Assn., 1913, lxi, 1254.
6 Goodman and Howell: Am. Jour. Med. Sc., 1911, cxlii, 324.
7 Warfield, L. M.: Ibid., 1914, cxlviii, 880.

The diastolic pressure measures the peripheral resistance. It measures the work of the heart, the potential energy,[8] up to the moment of the opening of the aortic valves. It is the actual pressure in the aorta. The diastolic pressure is not very variable; it is not subject to the same influences which disturb the systolic pressure. It fluctuates, as a rule, within a small range. It is not affected by diet, by mental excitement, by subconscious psychic influences, to anything like the extent to which the systolic pressure is affected by the action of these factors. The diastolic pressure is determined by the tone in the arterioles and is under the control of the vasomotor sympathetic system. Any agent which causes chronic irritation of the whole vasomotor system produces increase in the peripheral resistance with consequent rise in the diastolic pressure. Any agent which acts to produce thickening of the walls of the arterioles, narrowing their lumina, produces the same effect.

Such states naturally result in increased work on the part of the heart, which, as a result, hypertrophies in the left ventricle. The increase in size and strength is a compensatory process in order to keep the tissues supplied with their requisite quota of blood. Conversely, paralysis of the vasomotor system produces fall of diastolic pressure which, if long continued, results in death.

The diastolic pressure then is of importance for the following reasons:

1. It measures peripheral resistance.

2. It is the measure of the tonus of the vasomotor system.

3. It is one of the points to determine pulse-pressure.

4. Pulse-pressure measures the actual driving force, the kinetic energy of the heart.

5. It enables us to judge of the volume output, for pulse-pressure (PP) × pulse-rate (PR) = volume output in most instances.

6. It is more stable than the systolic pressure, subject to fewer more or less unknown influences.

7. It is increased by exercise.

8. It is increased by conditions which increase peripheral resistance.

9. The gradual increase of diastolic pressure means harder work for the heart to supply the parts of the body with blood.

10. Increased diastolic pressure is always accompanied by increased pulse-pressure and increased size of the left ventricle, temporarily (exercise) or permanently.

11. Decreased diastolic pressure goes hand in hand with vasomotor relaxation, as in fevers, etc.

12. Low diastolic pressure is frequently pathognomonic of aortic insufficiency.

13. When the systolic and diastolic pressures approach, heart failure is imminent either when pressure picture is high or low.

[8] Stone, W. J.: Arch. Int. Med., 1915, xvi, 775.

Pulse-pressure measures the actual head of pressure which maintains the circulation, the force driving the blood to the periphery. As the circulatory bed widens the pulse-pressure diminishes until at the capillaries it is only about 5 mm. Hg.

When all these factors are taken into consideration it becomes apparent that the diastolic pressure is most important, if not the most important, part of the pressure picture. I am not unaware of the value of the great mass of statistical evidence which shows the bad prognostic import of high systolic pressure alone. One could show by the red cell count alone the seriousness of the low count, but one would fail to differentiate types of anemia and be unable to offer really valuable evidences of the gravity of anemia. So while conclusions drawn from statistics of high systolic pressure are in general correct, there is necessarily much that is incorrect and grossly misleading in them. I feel that only when we study our cases with the whole pressure pictures before us will we be able to draw really valuable conclusions for everyday use.

Figures for the normal pressure picture vary somewhat with sex and age. In adults we may safely assume that a systolic pressure which is constantly over 150 mm. Hg. is abnormal; a diastolic constantly over 90 is abnormal and a pulse-pressure over 50 mm. is an increased pressure.

Normally the pulse-pressure varies from 30 or under, low to 50 or above, high. We have found that in all of the cases of high pulse-pressure the left ventricle was dilated—it actually held more blood than a normal ventricle holds. The arch of the aorta was also dilated, easily revealed by auscultating over the manubrium,[9] and the seat of a definite sclerosis which rendered it less capable of expansion when the blood from the left ventricle was thrown into it at systole. The sequence of events conjecturally is as follows: There is arteriosclerosis of the aorta (usually the nodular), diffuse thickening of the walls of the large arteries, also some concomitant fibrous change in the myocardium. The elasticity of the aorta is reduced, hence the evenly distributed force which normally keeps the blood moving between systoles is absent. In order for the circulation to be carried on out to the extreme periphery, so that all the organs receive blood, more blood must be thrown at each systole into the aorta. The force also must be greater because the distributing tubes are no longer capable of doing their full share in maintaining the circulation in equilibrium. This not only causes hypertrophy of the left ventricle but actual increase of size of the cavity of the ventricle in order to accommodate the added amount of blood which must be put out at systole. As a result the left ventricle hypertrophies and dilates. The pathological process which is present in the myocardium by its very nature tends to increase gradually. More muscle fibers

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[9] Warfield, L. M.: Jour. Am. Med. Assn., 1917, lxviii, 824.

are destroyed, more dilatation supervenes, more compensatory hypertrophy of the remaining fibers takes place. A vicious circle thus becomes established until finally the heart loses the power of carrying on the circulation and decompensation sets in. While we cannot prove this sequence absolutely, we believe that our clinical studies and our pathological studies make it more than probable that events occur in the order in which they have been related.

Again, the diastolic pressure, the peripheral resistance, does not rise in these cases above 110 mm. Usually it is between 90 and 100 mm. The systolic rarely goes above 200 mm. The pulse-pressure then may be from 80 to 110 mm. The larger the pulse-pressure the greater the cavity of the left ventricle and the more dilated is the arch of the aorta.

Stone[10] has divided the cases of hypertension into the cerebral and cardiac types. He finds there is a difference in prognosis and in mode of death in the two groups. He thinks that the pressure-ratio (heart load) which he has made use of will enable one to determine the type of case. I cannot say that I have found his method applicable except to a very few cases, although I agree with him in his contention that such a separation of cases is possible. I have felt the need of a better classification of the cases of chronic hypertension. For the past few years the cases have been critically studied, and it is believed that Stone's first group is composed of two groups, in general usually differentiable. I should therefore propose a classification into three groups. Syphilis is not an etiological factor in these cases. It is not contended that these groups are absolutely distinct. There are variations and combinations which render an exact separation into groups impossible. Bearing this in mind the following classification of the chronic high blood-pressure cases is submitted.

GROUP A. *Chronic Nephritis.* These are the cases with a high-pressure picture, that is to say, high systolic (200+) and high diastolic (120–140+). The pulse-pressure is much increased. The palpable arteries are hard and fibrous. There is puffiness of the under eyelids, which is more pronounced in the morning on arising. Polyuria with low specific gravity and nycturia are present. There are almost constant traces of albumin in the urine, with hyaline and finely granular casts.

Functionally these kidneys are much under normal. The functional capacity determined by Mosenthal's modification of the Schlayer-Hedinger method shows a marked inability to concentrate salts and nitrogen. The phthalein output is below normal. As the case advances the phthalein output becomes less and less until a period is reached when there are only traces or complete suppression

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[10] Loc. cit.

at the end of a two-hour period. Such patients may live for ten weeks (one of our cases), all the time showing mild uremic symptoms, and suddenly pass into coma and die.

The natural end of patients in this group is either uremia or cardiac decompensation (so-called cardiorenal disease). Cerebral accidents may happen to a small number. It is only to this group, in my opinion, that the term cardiorenal disease should be applied. Formerly I believed that all high systolic pressure cases were cases of chronic nephritis of some definite degree. From the purely pathological stand-point that is true, but from the real, the functional stand-point, it is far from being the true state of the cases.

In this group there is marked hypertrophy and moderate dilatation of the left ventricle with dilatation and nodular sclerosis of the aorta. The kidneys are firm, red, small, coarsely granular, the cortex much reduced, the capsule adherent. Cysts are common. It is the familiar primary contracted kidney. Mallory calls this capsular-glomerulo-nephritis. The etiology is obscure. Often no cause can be found. Again, there is a history of some kidney involvement following one of the acute infectious diseases, or it may follow the nephritis of pregnancy. Usually, however, these cases fall into the group of secondary contracted kidneys, chronic parenchymatous nephritis.

CASE I.—R. Z., a woman, aged thirty-six years, was seen July 26, 1916, in coma. There was a history of typhoid fever at nineteen years, but no other disease. She had had nine full-term pregnancies, the last one thirteen months previously. For a week before the onset of the present illness she had complained of severe headaches and dizziness. There were no heart symptoms. For the past year she has had nycturia. Physical examination revealed tubular breathing beneath the manubrium, a few rales in the chest, an enlarged heart (left side), with a systolic murmur over the aortic area. Blood-pressure was 178–125–53, the pulse-rate 96, leukocytes 27,250. Venesection of 500 c.c. of blood and intravenous injections of 500 c.c. of 5 per cent. $NaHCO_3$ in normal saline were employed. Lumbar puncture withdrew 60 c.c. of clear fluid under pressure with 6 cells per cubic millimeter. The eye-grounds showed distinct haziness of the disks and dilatation of the veins. Blood-pressure after venesection was 164–122–42, pulse 76, but in a few days rose to 222–142–80, pulse 70. A second venesection of 400 c.c. and proctoclysis of 1000 c.c. saline solution was tried. The blood-pressure now was 198–140–58. The pH of the blood was 7.6, the alkaline reserve was 35 volume per cent. (van Slyke), and the CO_2 tension of the alveolar air (Marriott) was 25 mm. The phthalein on the day following the second venesection was 45 per cent. in two hours. The urine at first showed 500 c.c. in twenty-four hours, specific gravity 1016, albumin and casts. Later she passed 1300 to 1600 c.c., with specific gravity around 1010. The

blood-pressure fluctuated considerably, reaching as low as 138–98–40, pulse 88. She was discharged improved September 10, 1916. At present (March, 1917) she is doing all her housework, but occasionally has headaches and attacks of dizziness.

GROUP B. This one might designate as the hereditary type, although there is not always a history in the antecedent. This group includes the robust, florid, exuberantly healthy people. They often are heard to boast that they have never had a doctor in their lives. They are usually thick-set or very large, fleshy people. The pressure picture is exceedingly high. The pulse-pressure is moderately increased. The arteries are rather large, fibrous, and often quite tortuous, although this is not always the case. Some persons have hard, small fibrous arteries. There is no puffiness beneath the eyes, no polyuria, and no nycturia as a rule. The urine is of normal amount, color, and specific gravity. Albumin is only rarely found and then in traces, but careful search of a centrifuged specimen invariably reveals a few hyaline casts. The phthalein excretion is normal or only slightly reduced. The kidneys excrete salt and nitrogen normally. It is in this group that apoplexy is found most frequently. The rupture of the vessel occurs when the victim is in perfect health, often without any warning. Occasionally when such a case recovers sufficiently to be around, cardiac decompensation sets in later and he dies then of the cardiac complications.

Pathologically the hearts of such persons are found to have the most enormous hypertrophy of the wall of the left ventricle. The cavity is somewhat enlarged, as is always the case when the pulse-pressure is increased, but the size of the cavity is not the striking feature. The aorta is fibrous, thick walled, and the arch is slightly dilated. There are patches of arteriosclerosis. One such case seen only at autopsy had a rupture of the aorta just above the sinus of Valsalva and died of hemopericardium. The kidneys are of normal size, dark red, firm, the capsule strips readily, the surface is smooth or finely granular, the cortex is not decreased. The pyramids are congested and red streaks extend into the cortex. Microscopically the capsules of the glomeruli are a trifle thickened; a few show hyaline changes. There is rather diffuse, mild, round-cell infiltration between the tubules. The tubular epithelium shows little or no demonstrable changes. The arterioles are generally the seat of a moderate thickening of the intima and media, but it is not usual to find obliterating endarteritis. There is evidently a diffuse fibrous change which has not affected either the tubules or glomeruli to any great extent.

CASE II.—L. C., a man, aged fifty-six years, stonemason by trade, is a stocky, thick neck individual. He has never been ill in his life until a year ago, when he fell from his chair unconscious. He had a right-sided hemiplegia which has cleared up so completely that except for a very slight drag to his foot he walks

perfectly well. He came in complaining of shortness of breath and cough. There was no swelling of the feet. Here evidently was left-heart decompensation. Examination showed the blood-pressure to be 240–130, pulse irregular, 104 to the minute. There was cyanosis and rales throughout both chests. The urine was normal in color, specific gravity 1025, small amount of albumin, few casts, hyaline and granular. The phthalein elimination was 65 per cent. in two hours. Under rest, purgatives, and digitalis he was much improved. He has since had two other apoplectic strokes, the last of which was fatal.

When these patients are seen with acute cardiac decompensation there is, of course, much albumin and many casts in the urine, and the phthalein output is, for the time being, decreased.

Group C. This might be called the arteriosclerotic high-tension group. The cases are usually over fifty years old. They are men and women who have lived high and thought hard. Often they have had periods of great mental strain. Many men in this group were athletes in their young manhood. Many have been fairly heavy drinkers, although never drinking to excess. They are usually well nourished and inclined to stoutness. The pressure picture is high systolic with normal or only slightly increased diastolic and large pulse-pressure. The arteries are large, full, fibrous, usually tortuous. The heart is very large, the apex far down and out. There is no polyuria; nycturia is uncommon, quite the exception. The urine is normal in color, amount, and specific gravity. Albumin is only rarely found and hyaline casts are not invariably present. The phthalein excretion is quite normal and the excretion of salt and nitrogen are also normal. The terminal condition in most of the patients in this group is cardiac decompensation. They may have several attacks from which they recover, but after every attack the succeeding one is produced by less exertion than the preceding one, and it becomes more and more difficult to control attacks. Eventually the patients become bed- or chair-ridden, and finally die of acute dilatation of the heart.

Occasionally patients in this group may have a cerebral attack, but in my experience this is uncommon. Pathologically the heart is large, at times true cor bovinum, dilated and hypertrophied. The cavity of the left ventricle is much dilated. The aorta is dilated and sclerosed.

The kidneys are increased in size, are firm, dark red in color, with fatty streaks in the cortex. The capsule strips readily and the cortex is normal in thickness or only slightly increased. The organ offers some resistance to the knife. The microscope shows small areas scattered throughout where the glomeruli are hyalinized, the stroma full of small round cells, the tubules dilated, and the cells are almost bare of protoplasm. Naturally the tubules are full of granular cast material. Also the arterioles show extensive intimal

thickening, fibrous in character, with occasional obliterating endarteritis. One gets the impression that the small sclerotic lesions are the result of anemia and gradual replacement of scattered glomeruli by fibrous tissue. For the most part the kidney, except for the chronic passive congestion, appears quite normal. One can readily understand that in such a kidney function could not have been interfered with.

CASE III.—C. K., an active, stout, business man, aged fifty-six years, consulted me on account of shortness of breath and swelling of the feet in May, 1915. He had just returned from a hospital in another city, where he had gone with what was apparently cardiac decompensation. In his early manhood he had been a gymnast and was a prize winner. He has worked hard, often given way to violent paroxysms of temper, has eaten heavily but drunk very moderately. The heart was greatly enlarged, the arch of the aorta dilated, a mitral murmur was audible at the apex. The radials and temporals were large, tortuous, and fibrous. The blood-pressure picture ranged around 180–90–90. He was easily made dyspneic and had a tendency to swelling of the lower legs. The urine was acid, of normal specific gravity, normal in amount, normal phthalein, normal concentration of salt and nitrogen, contained albumin only when he was suffering from decompensation of the heart. Casts were always found. He finally died, after sixteen months, with all the symptoms of chronic myocardial insufficiency. The heart was enormous, a true cor bovinum. The kidneys were typical of this condition, possibly somewhat larger than usual.

The management of these groups of patients presents many difficulties. I believe that all these excessive pressures are compensatory. As has been said before, the systolic pressure is subject to considerable variations, but the diastolic remains fairly constant. Unless one can reduce the whole pressure picture therapy is useless. This reduction is far from being easy to accomplish. Occasionally one sees cases, such as two we have seen, in which there was uremia, high-pressure picture, almost total phthalein suppression. Eventually there was complete recovery, with normal pressure pictures. Such cases are the exceptions and are probably acutely toxic in origin. The chronic, slowly progressive cases do not act thus. The best we can do is to make searching inquiries into the mode of life and regulate it on a rational basis. All people of the three groups need regulation of habits and diet. We have not found drugs of value, with the possible exception of bichloride of mercury and potassium iodide. Even in the positive absence of syphilis these drugs in combination seem to exert a favorable influence on the factors which are causing the high pressure. Electricity in the form of the static current, the high-frequency current, and other forms are recommended. All aid in maintaining nutrition and hygiene, but in my experience have no permanent effect upon this class of cases which other measures do not have.

Naturally when decompensation sets in it is to be treated as it usually is in spite of the high systolic and high diastolic pressure. As a matter of fact I have seen the pressure picture reduced when compensation was restored under digitalis, and it is generally recognized that such is the case. Personally I believe that hydrotherapy, attention to the bowels, regular hours, great decrease in food, limitation of meats, especially purin base-containing meat products, substitution of buttermilk and cheese in the diet, are the chief means at our disposal for regulating the lives of those who fall into our hands before accidents have happened. But I realize that we have no means of actually preventing a cerebral hemorrhage, although we have some control over the development of a cardiac breakdown.

Finally, this grouping is of interest in respect to prognosis. Careful examination of the patient should enable us to predict with some degree of accuracy what will happen to him. We may be able to modify somewhat the course, and, in general, we can render a fairly correct prognosis. This is certainly of value to the patient's family as well as to the patient.

CONCLUSIONS. 1. In a blood-pressure reading the whole record should be taken, systolic, diastolic, pulse-pressure, and pulse-rate. The pressure picture is the term suggested for the figures representing the component parts of the blood-pressure reading.

2. The diastolic and pulse-pressure give us more information than the systolic pressure.

3. There are three groups of high-pressure cases, called (A) chronic interstitial nephritis, (B) hereditary or cerebral type, (C) arteriosclerotic or cardiac type. Causes of death are usually anemia in group A, cerebral hemorrhage in group B, and cardiac decompensation in group C.

4. The term cardiorenal disease should be reserved for the cases of group A, which suffer from cardiac decompensation; the term hypertensive cardiovascular disease for cases of group B. Myocardial insufficiency covers most of the cases in group C.

5. Prognosis is much more intelligently given when this grouping of cases is followed.

A STUDY OF CASES OF ASCITES IN THE WARDS OF THE CANTON HOSPITAL, CHINA.

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CANTON, CHINA.

A visitor to the medical wards of the Canton Hospital is always impressed with the large number of patients suffering from ascites. While the majority of patients admitted to the hospital are surgical, yet we find that during thirteen months from March, 1914, to April, 1915, 3.95 per cent. of all admissions were cases of ascites. This was out of a total of 2250 admissions. Excluding all general surgical cases and eye, ear, nose, throat, and neurological patients, in whom there were no cases of ascites, we have left 452 patients admitted to the medical wards during a period of eight months. Of these 70, or 17.69 per cent., were suffering from ascites..

It must be borne in mind that the prevalence of any disease among the Chinese cannot be determined by hospital statistics. A large proportion of medical cases are never sent to an institution but are treated at home by an old-style Chinese physician. Surgery being an unknown art to these, a much larger percentage of surgical cases are sent to the practitioner of western medicine. The Chinese doctor stands helpless before a case of advanced ascites, while he believes that his decoctions will have a beneficial effect upon other medical conditions.

Nevertheless, it is our belief that those pathological processes which lead to the accumulation of free fluid in the abdomen are unusually prevalent among the Chinese of Canton and its environs, and it was with this in view that the present study was undertaken.

At the start it should be made clear that our data were collected under many difficulties. The histories are not always complete. Blood and urine examinations were omitted in some cases, and the modern procedures of electrocardiography and renal function tests could not be employed at all. A physical examination was made, however, in every patient, and upon this alone the diagnosis must rest in some. We are assured that free ascitic fluid was present in all the cases reported.

The present paper is based on data obtained from 80 patients, all of whom had ascites from some cause. Several were admitted to the hospital two or three times, and the period of residence varied from a few hours to several months. These 80 cases have been classified under eight heads, in accordance with the dominant pathological lesion, so far as it could be determined, without an autopsy. These eight groups are as follows:

Predominant lesion.	Cases.	Percentage.
Hepatic disease	22	27.5
Splenomegaly	13	16.25
Hepatic disease and splenomegaly	5	6.25
Nephritis	21	26.25
Heart disease	10	12.5
Nephritis and heart disease	3	3.75
Tuberculous peritonitis	4	5.0
Abdominal tumors	2	2.5
Total	80	100.0

The nationality of all these cases was Chinese. Only patients who were admitted to the wards are considered. For the present we shall confine our attention to the first six groups, leaving the tuberculous cases and the abdominal tumors for later study.

DIFFERENTIAL DIAGNOSIS. Of the 22 cases of hepatic disease there was definite clinical evidence of some pathological process in the liver in only 6, in which there was marked enlargement, local tenderness, or jaundice. The remaining cases were classified as hepatic disease, probably atrophic cirrhosis, because of the absence of definite signs of lesions in other organs that might produce ascites.

In 13 cases there was marked enlargement of the spleen without signs of liver involvement.

In 5 cases both spleen and liver were enlarged or there was spleno-megaly with jaundice. Some of this group might fairly be classified as Banti's disease.

The 21 cases of nephritis were characterized by albuminuria or other signs suggesting chronic interstitial nephritis.

In 10 cases there was no definite abnormality in the urine, but there were present signs of endocarditis or myocarditis.

In 3 patients there was marked albuminuria associated with organic heart disease. Enlargement of the liver or spleen when it occurred in the cases classed as cardiac appeared to be the result of chronic passive congestion.

Age.

	Under 20 years.	20 to 39 years.	40 to 60 years.
Hepatic	2	10	10
Splenomegaly	0	9	4
Hepatic and splenic	0	4	1
Nephritis	2	15	4
Cardiac	0	5	5
Cardiac nephritis	0	3	0

All of the cases were between the ages of nineteen and sixty years except one child of three, with acute nephritis. The hepatic and cardiac cases showed about equal numbers before and after the fortieth year. There were more than four times as many cases of nephritis under forty years of age as over, indicating that this condition is more prone to affect young adults. Splenomegaly was also more common in the third and fourth decades than in the fifth

and sixth. Our series indicates that ascites is rarely found in the Chinese under nineteen years of age unless it be caused by tuberculous peritonitis.

Sex.   Only 18 of the 80 cases were female. Of these 4 had tuberculous peritonitis or abdominal tumors, 1 splenomegaly, 4 cirrhosis of liver, 4 nephritis, 4 heart disease, and 1 cardiorenal disease. Excluding the cases of tuberculous peritonitis and abdominal tumors, 81 per cent. of the patients were males and 19 per cent. were females.

Place of Birth.   Many patients came from towns and villages at a distance from Canton, but all but 6 came from the province of Kwangtung.

Nineteen men and four women were recorded as unmarried.

OCCUPATION OF SEVENTY CASES.

Occupation.	Hepatic.	Splenic.	Hepatic-splenic.	Nephritic.	Cardiac.	Cardio-renal.	Totals.
Printer	. .	. .	. .	. .	1	. .	1
Student	. .	. .	. .	1	. .	. .	1
Farmer	8	3	2	1	1	2	17
Shopkeeper	4	1	. .	4	2	. .	11
Sailor	1	2	. .	. .	. .	. .	3
Soldier	1	1	. .	3	1	. .	6
Teacher	. .	. .	. .	1	2	. .	3
Gambler	. .	. .	1	. .	. .	. .	1
Laborer	3	4	1	6	1	1	16
Clerk	. .	. .	. .	2	. .	. .	2
Housework	2	. .	. .	1	. .	. .	3
Dressmaker	. .	. .	. .	. .	2	. .	2
Painter	1	. .	. .	. .	. .	. .	1
Weaver	. .	. .	1	. .	. .	. .	1
Cook	. .	1	. .	. .	. .	. .	1
Child (3 years)	. .	. .	. .	1	. .	. .	1

The list of occupations throws but little light on the etiology of ascites. The great majority of patients admitted to the hospital are farmers, laborers, or shopkeepers. It is striking that most of the patients lived in the country and had spent but a few years at most in the city.

Family History.   The family history was often unreliable and the causes of death of parents or other relatives were difficult to ascertain. One case of cirrhosis of the liver reported that his father died of dropsy. Of the splenomegaly cases the father of one died of edema and the sister of another died from the same cause. In a patient with enlarged spleen and liver the mother was reported to have died of heart disease. Four of the twenty-one nephritics reported a suggestive family history, and one of the cardiac cases stated that his mother died of edema. Thus in only 9 of the 74 patients could any definite family history bearing on the present disease be obtained.

Previous Disease. These records are not complete in regard to previous history. There were 9 who reported attacks of chills and fever, 4 had had dysentery. There is no doubt that malaria is an important factor in the causation of many cases of splenomegaly, but more especially cases not complicated with ascites. Dysentery was more frequently an initial symptom than a previous illness. The nephritis cases showed a tendency to relapse. Four had had previous attacks, each followed by temporary recovery. We have personally observed patients suffering from marked parenchymatous nephritis of the chronic type, in which all signs of disease, including albuminuria, have entirely disappeared. Twenty-nine out of 40 cases denied venereal infection, but a Wassermann test was not made, and undoubtedly more were infected.

ALCOHOL AND OPIUM. ALCOHOLISM IN 47 CASES OF ASCITES.

	Hepatic.	Hepatic-splenic.	Spleno-megaly.	Nephritis.	Cardiac.	Cardio-renal.
Total abstainer . . .	0	0	1	1	1	1
Takes less than 500 c.c. daily	9	4	3	9	3	2
Takes more than 500 c.c. daily	4	0	2	2	5	0
Percentage of cases using alcohol	100.0	100.0	83.3	91.6	88.8	66.6

Alcohol is drunk as rice wine generally. This may vary in strength from 4 per cent. up. Drunkenness is rare, but drinking is practised pretty generally. Though we have no data on this subject in a number of cases studied, yet our table indicates that in cirrhosis of the liver, with ascites at least, alcohol is probably an etiological factor.

Only 5 of the patients were opium smokers. We cannot assign therefore any great importance to the use of this drug.

The mode of onset of the disease was determined by careful questioning in most cases. When disease of the liver or spleen was the underlying cause, abdominal enlargement was usually the first marked sign. In affections of the heart and kidney edema of the legs was generally the first thing noted. In 6 cases the disease was ushered in by an intitial attack of diarrhea or dysentery.

DURATION AND RESULT OF DISEASE.

	Duration of illness before admission to hospital in 71 cases.					Time spent in hospital in 74 cases.						Result in 73 cases.				
	Under 1 mo.	1 to 2 mos.	2 to 6 mos.	6 mos. to 1 yr.	1 to 2 yrs.	2 to 15 yrs.	1 to 7 days	7 to 14 days.	2 to 3 wks.	3 to 4 wks.	1 to 2 mos.	2 to 4 mos.	Recovered.	Much improved.	Improved.	Unimproved.	Death.
Hepatic	8	4	4	2	0	3	7	5	2	7	0	1	2	5	8	2	4
Splenic	2	4	2	1	2	2	2	3	0	4	4	0	0	7	4	0	2
Hepatic-splenic . . .	0	2	1	0	0	2	1	0	2	1	1	0	0	1	2	1	1
Renal	2	5	5	6	1	1	5	3	0	5	8	0	0	9	9	0	3
Cardiac	2	2	4	1	0	0	2	4	1	2	0	1	1	4	2	0	3
Cardiorenal . . .	1	1	0	0	1	0	1	0	0	0	2	0	0	1	0	0	2

It will be noted by examining the above table that many cases had been suffering for weeks or months before admission to the hospital. A few cases died a few days after admission, but the majority remained for one or more weeks, giving sufficient time for study and diagnosis. It may not be correct to speak of recovery in patients with ascites. However, 2 of the hepatic cases and 1 heart case left the hospital free of symptoms. The most satisfactory results were obtained in the renal cases. There was less tendency for the ascitic fluid to recur, although albuminuria generally persisted.

Unfortunately, no autopsies could be performed, but the cause of death was usually quite evident. Two of the hepatic cases that died were not tapped. One had a terminal enteritis and the other showed marked jaundice, and delirium. Another patient died of a probable abscess of the liver. Two with splenomegaly died. One of these became delirious soon after aspirating the fluid, and remained in this condition until death. The other, a young woman, from whom 15,000 c.c. of fluid were removed, died twelve hours later in collapse.

There were 2 cases of cirrhosis, or enlargement of the liver and splenomegaly, who died. In 1 case there was an abscess of the liver which ruptured into the lung. The other died shortly after leaving the hospital with symptoms of cerebral embolism which followed aspiration.

One of the cases of nephritis became uremic after the second aspiration and died.

Of the patients with heart disease 1 died with signs of cerebral embolism which came on soon after tapping the abdomen. One who was not tapped showed signs of beriberi. The third heart case, who had aortic incompetency, died soon after aspiration.

Two patients with advanced heart and kidney disease died. One showed marked jaundice and toxemia and the other died of advanced mitral disease with decompensation.

Temperature. A normal or subnormal temperature was usual. There were 18 cases in whom the thermometer reached as high as 100°. In 7 cases it reached 101°. In 4 cases it rose to 102° or above.

Twenty-six of the case histories gave no record of the condition of the heart. It may be assumed that in these there was no heart disease or at most a functional impairment.

In 3 of the patients with splenomegaly a mitral systolic murmur was heard, probably functional. In 5 of the patients with nephritis there were signs of heart disease, but the renal symptoms were decidedly predominant.

There were 10 cases, however, in which the ascites was considered as a complication of organic heart disease. Seven of these showed mitral regurgitation, 2 aortic regurgitation, and 1 evidence of myocarditis.

THE CIRCULATION.

	Blood-pressure (systolic).													Rate of pulse.											Condition of heart.								
	No record.	60	80	100	110	115	120	130	150	170	180	200	225–235	No record.	55	65	70	75	80	90	95	100	110	120	No record.	Feeble.	Accentuation of 2d aortic.	Hemic murmur.	Tricuspid systolic.	Aortic diastolic.	Mitral systolic.	Mitral diastolic.	Normal.
Hepatic	17	.	.	1	2	.	2	.	.	.	.	.	.	3	.	.	0	2	7	3	.	4	.	3	15	0	0	0	0	0	0	0	7
Splenic	8	.	.	.	1	2	.	2	.	.	.	.	.	4	1	.	1	1	6	.	.	.	.	.	4	1	0	0	0	0	3	0	5
Hepatic and splenic	1	.	.	2	1	.	1	.	.	.	.	.	.	0	.	.	1	.	3	.	.	1	.	.	0	0	0	0	0	0	1	0	4
Renal	10	2	.	.	.	2	1	1	1	2	1	1	.	4	.	1	1	.	7	5	1	2	1	.	7	1	1	0	1	0	3	1	7
Cardiac	1	.	1	2	.	.	2	2	1	.	.	.	1	1	.	.	1	.	5	2	.	.	.	.	0	1	0	0	0	2	7	0	0
Cardiorenal	1	.	.	.	.	1	1	.	.	.	.	.	.	2	.	.	0	.	.	.	.	1	.	.	0	0	0	1	0	0	2	0	0

Out of 452 patients admitted to the medical wards of the hospital in 1914, 19 were diagnosed as heart disease, and 5 of these, or 26.3 per cent., had ascites.

The pulse-rate was not generally increased above 80. Excessive accumulation of ascitic fluid caused embarrassment of the heart and a consequent acceleration of the pulse.

The systolic blood-pressure was estimated in several cases. The Nicholson apparatus was used. The highest reading was found in a case of aortic regurgitation.

In general, aspiration of fluid has no appreciable effect on high pressure. There might be a temporary fall, but the next day it returned to the original reading; except in one instance of aortic regurgitation the higher readings were found in cases of nephritis.

HEMOGLOBIN IN THIRTY–FOUR CASES.

	90 to 100 per cent.	80 to 89 per cent.	70 to 79 per cent.	60 to 69 per cent.	50 to 59 per cent.	20 to 29 per cent.
Hepatic	..	1	2	1		
Splenic	..	2	3			
Hepatic and splenic	1	3				
Renal	1	2	3	4	2	1
Cardial	..	2	3	1		
Cardiorenal	..	2				

Anemia is especially marked in the nephritic cases, more than half of which were below 70 per cent.

Respiratory System. The records of the lungs and respiratory organs were not complete. There was no case of pneumonia. In the majority of patients there was marked dyspnea on admission because of the intra-abdominal pressure. This usually soon disappeared after aspiration. In only 4 was there evidence of pleural effusion: three on the left and one on the right side. The effusions were moderate and did not require tapping.

Liver. Enlargement of the liver was noted in 7 cases. In 2 there was tenderness, but in only 1 was an abscess demonstrated. In this last case the pus discharged into the lungs. There was a marked infection of clonorchis sinensis. In several instances it was not definitely stated whether the liver was enlarged or not. It is probable that in most of these it was of normal size or reduced.

Spleen. The spleen was noted as enlarged in 19 cases, in 1 of which the enlargement was apparently caused by passive congestion. Excluding this there were only 18 cases, or 24 per cent., with splenomegaly; 4 of these cases appeared to be Banti's disease. Among the others 1 was diagnosed cancer of the spleen, in 3 there was a history of malaria, and in 1 of excessive alcoholism. The spleen did not average as large as in many cases of splenomegaly without ascites.

Digestive System. Pressure of the fluid on the stomach and intestines always caused marked digestive disturbance. Severe

enteritis was a frequent complication. In 1 patient with nephritis and marked albuminuria, suppression of urine was difficult to overcome until a violent acute enteritis developed, when the urinary output was markedly increased.

OVA OF INTESTINAL PARASITES.

	No record.	No ova.	Ankylostoma.	Ascaris.	Tricocephalus.	Ascaris, ankylostoma, tricocephalus.	Ascaris, clonorchis sinensis.	Clonorchis sinensis.	Clonorchis tricocephalus.	Clonorchis ankylostoma.
Hepatic	16	4	..	1	1					
Splenomegaly	6	3	2	1	..	..	1			
Hepatic and splenomegaly	1	1	..	..	1	..	..		..	
Renal	9	4	1	3	2	..	..	1	1	2
Cardiac	2	7	..	..	..	..	1			
Cardiorenal	..	..	1	..	1	1				

It is to be regretted that the feces were not examined in all of the patients. There were 40, however, in whom ova were looked for and there was evidence of parasites in about one-half of these. Ankylostoma and clonorchis sinensis by their own pathological processes producing either a profound anemia on the one hand or extensive disease of the liver on the other, may be directly responsible for the ascites. Hookworms were present in 7 cases while clonorchis was found in 6. In 2 of the latter there was great abundance of ova in the feces, and there was marked tenderness over the liver.

The Urine. In all patients in whom albuminuria was marked a diagnosis of nephritis was made. In 2 cases there were signs of chronic interstitial nephritis, but no albumin was found in the urine. In 15 cases with nephritis there was a heavy precipitate of albumin, the amounts varying from 0.5 gm. to 10 gms. excreted per 1000 c.c. of urine. Granular and hyaline casts were generally found in these cases.

Ascites resulting from Bright's disease is almost always associated with marked albuminuria. The urine is often very scanty, only 100 c.c. to 500 c.c. being voided in the twenty-four hours. It was observed that in favorable cases the disease appeared to remain stationary for a time until a crisis, so to speak, occurred, when the urine increased in quantity and ascitic fluid ceased to accumulate in the abdomen. This critical change was brought about in some cases after the first or second tapping, in other instances the improvement took place some days or weeks after removing the ascitic fluid. In unfavorable cases retention of urine and symptoms of uremia followed soon after the aspiration of the abdominal fluid.

In the hospital report for 1914 there appear but 32 cases of nephritis, and according to our series 21 of these showed more or less ascitic fluid.

EDEMA RECORDED IN SIXTY CASES.

	None.	Legs and feet only.	Feet and scrotum.	Face and feet.	General anasarca.
Hepatic	3	9	2	..	1
Splenomegaly	5	4	0		
Hepatic and splenomegaly	2	2	0		
Renal	..	3	3	1	12
Cardiac	..	6	..	..	4
Cardiorenal	1	1	1		

It is very evident from the above table that in cases of nephritis ascites is likely to be part of a general anasarca. When edema appeared in cases of cirrhosis of the liver or splenomegaly it was usually caused by pressure on the lower extremities and was soon relieved by removing the cause.

In the heart and kidney cases this was not so generally the case. If a free flow of urine was not established by tapping the edema persisted or quickly returned.

If the edema disappeared in renal cases after aspirating the abdomen a favorable prognosis was justifiable, but if the edema persisted there was little prospect of recovery.

The frequent occurrence of edema in cases of nephritis among the Chinese is of special interest because of recent studies of the effect of sodium chloride on this disease. It is well known that the best method of treating the edema of Bright's disease is by giving a diet free of salt. Now, salt among the Chinese is a luxury seldom indulged in by the lower classes. Rice, the main diet, is cooked and eaten without any salt. Meat is eaten in very minute portions by the laborer, and vegetables are likewise prepared without salt. We have, therefore, to do with a people who rarely eat salt and whose diet is almost purely vegetarian, and yet afflicted with a severe form of nephritis frequently accompanied by local edema, ascites, or general anasarca. In this connection it is also of interest to note that the dairy products—milk, butter, and cheese—do not form part of the dietary of the average Chinese.

Ascites caused by disease of the heart and kidneys is often relieved by appropriate treatment of these organs and the fluid does not have to be withdrawn so often as in patients suffering from cirrhosis of the liver or splenic enlargement. In 2 of the hepatic cases in whom the fluid was not withdrawn there was a large amount present, but the patients being *in extremis* no operative procedure was ventured upon. The largest amount of fluid was found in 2 cases of cirrhosis, in 1 of which 20 liters and in the other $16\frac{1}{2}$ liters were removed at the first tapping. It was generally found necessary to aspirate when the fluid reached between 5 and 10 liters. Less than this amount caused comparatively slight discomfort, and more produced much oppression with nausea and vomiting.

Many cases are reported as being tapped but once, but in some cases there was a gradual reaccumulation of fluid. In only 4 was there no tendency to recurrence after tapping. In 9 the fluid was

DATA REGARDING ASCITIC FLUID IN SEVENTY-FOUR PATIENTS.

	Maximum amount of fluid drawn at one time.							Average amount of fluid when tapped more than once.			Number of times aspirated.							No tendency to recur after tapping.	Spontaneous disappearance.	Not aspirated.
	15,000 to 20,000 c.c.	10,000 to 15,000 c.c.	5000 to 10,000 c.c.	4000 c.c.	3000 c.c.	2000 c.c.	Under 1000 c.c.	10,000 to 20,000 c.c.	5000 to 10,000 c.c.	5000 c.c. or less.	Times not recorded.	Six times.	Five times.	Four times.	Three times.	Twice.	Once.			
Splenomegaly		2	6	1					4		1				2	3	5		2	2
Hepatic and splenomegaly			1	1		1			1		1	1					3			
Renal		3	5		1	1		1	5	1	1			1	1	7	6	1	4	5
Cardiac		1	2	1	1		1		2		2			1		1	4	2	3	4
Cardiorenal			1	2					1	1	1		2				1			
Hepatic	2	2	2	3				2	1	1	6			1		4	7	2		3

gradually absorbed, but in these there was at no time a very large amount.

TREATMENT. Diuretic drugs had little effect. When large amounts of ascitic fluid were present no relief was obtained until this was drawn off. The urinary output then increased and edema rapidly disappeared. Compound jalap powder proved to be the most satisfactory purgative. Little benefit was derived from hot sweat baths. Unfortunately due attention was not paid to the dietetic treatment of these cases.

TUBERCULOUS CASES. There were 4 patients with tuberculous peritonitis and ascites. Two were in children aged about fourteen, a boy and a girl, and two in adults, a man aged twenty-three and a woman forty-three. In three the abdominal distention was the primary condition with chills and fever. The woman gave a history of a long-standing pulmonary lesion. Abdominal section was performed in two. One, a child, was improved. The man of twenty-three was operated upon because of the very rapid accumulation of fluid. Only temporary relief was afforded, and he died on the sixteenth day after admission. All of these 4 cases ran a febrile course with rapid pulse. In the two adults tubercle bacilli were found in the sputum. Edema was absent or very slight.

PELVIC TUMORS. In two women ascites was associated with tumors of the genitalia. From one 4000 c.c. of clear fluid were aspirated before the diagnosis was made. The liver was enlarged. Operation was refused. The other case was a widow, aged forty-one years. On admission 10 liters of dark brown fluid were withdrawn, containing many cholesterin crystals. Upon abdominal section, later, an extensive carcinomatous growth was found, involving tubes, ovaries, and the peritoneum. A panhysterectomy was performed. Patient made a good recovery and was discharged from the hospital well after four months.

CONCLUSIONS. 1. Ascites is a common condition in the medical wards of a hospital in Canton.

2. This condition is most frequently associated with cirrhosis of the liver or chronic nephritis, but splenomegaly, heart disease, tuberculous peritonitis, and abdominal tumors are also causative factors.

3. The male sex is more prone to this form of disease than the female, and most cases occur between the twentieth and sixtieth years.

4. The majority of cases with ascites give an alcoholic history.

5. Although the Chinese are largely vegetarian in their diet, and seldom eat salt, nephritis associated with edema is by no means uncommon.

6. Ascitic fluid tends to recur after tapping, especially in cases of cirrhosis of the liver and splenomegaly. The best results were obtained when the ascites was caused by heart or kidney disease.

REVIEWS

LIFE OF DR. LYMAN SPALDING. By DR. JAMES ALFRED SPALDING. Pp. 367. Boston: W. M. Leonard, 1916.

THE author, a grandson of the subject of the biography, came within recent years upon a collection of papers, chiefly of letters, left by his grandfather, who lived from 1775 to 1821. They are, indeed, "a treasure for illuminating American medical history" of this early period, and this biography well deserves a place of honor in the libraries of medical men. Lyman Spalding was a protege and later a colleague of the famous Nathan Smith, the surgeon, who founded the Dartmouth Medical School, and father of the more famous surgeon, Nathan R. Smith. Dr. Spalding graduated from the Harvard Medical School in 1797, then taught chemistry for two years in the new Dartmouth Medical School, practised thirteen years in Portsmouth, N. H., spent one year (1809–1810) attending medical lectures in Philadelphia, lectured on anatomy and surgery in and was president of the Medical School in Fairfield, N. Y., for two years (1810 to 1812), and practised four years in New York. He played an important part in the introduction of vaccination into this country, and was the first physician in the country to read a paper on a National Pharmacopœia and to offer a working basis for its foundation. Although a committee was appointed to carry out his idea, he did nearly all the work personally, and carried the book through to its publication and sale. He developed a wide acquaintance among the most prominent members of the profession of his time, especially in this country, but also in England and France, and his numerous letters from these men come now as a very valuable contribution to the history of early American medicine.   H. D.

ANATOMICAL NAMES. By A. C. EYCLESHYMER, Head of Department of Anatomy of the University of Illinois. Pp. 774. New York: William Wood & Co., 1917.

THE value of the work done by the German Commissions appointed in 1887 to simplify the terms employed in the science of anatomy is now well established, and its name, the "Basle Nomina Anatomica,"

or its official abbreviation, BNA, needs no explanation. To maintain a familiarity with the recent anatomical literature we must be familiar with this system. The author, with the aid of D. M. Schoemaker, professor of Anatomy, of St. Louis University, presents the system with an English translation of the Commission's report, adopted more than twenty years ago. There is added a collection of some twenty thousand synonyms, each of which bears numerals citing the equivalent BNA term. There also has been included a biographical list, containing some eight hundred brief sketches of the leading anatomists of the whole world, which was prepared by Roy L. Moodie, assistant professor of anatomy of the University of Illinois. English anatomists and all those interested in the modern literature of anatomy will appreciate the value of this aid in their work.   T. T. T.

DISEASES OF CHILDREN. By GEORGE M. TUTTLE, M.D., Clinical Professor of Pediatrics, Washington University, St. Louis, and PHELPS G. HURFORD, Assistant in Pediatrics, Washington University, St. Louis. Third edition. Pp. 584; 47 engravings and 4 plates. Philadelphia: Lea & Febiger, 1917.

THIS volume is more properly a manual of the diseases of children, extremely concise, compact, very well arranged, and classified. The authors have, in this edition, thoroughly revised the former views, incorporated new scientific investigations from the literature and added much from personal and hospital observations.

It is more practical than a scientific text-book. A handy and ready reference book for both student and practitioner.

                                                                J. D.

TRAUMATIC SURGERY. By JOHN J. MOORHEAD, B.S., M.D., F.A.C.S., Adjunct Professor of Surgery, New York Post-Graduate Medical School and Hospital. Pp. 736. 522 illustrations. Philadelphia and London: W. B. Saunders Company, 1917.

THE presentation of a book devoted to traumatic surgery is opportune at this time because of the increased claims for damages under the compensation laws and the requirements of war surgery, so much of which is to be done by general practitioners who have not had special training for this work. The book is purposely didactic and follows the course of clinical lectures given by the author. The injuries of the various parts and tissues of the body are considered.

Arthroplasty as practised by the late John B. Murphy is strongly presented by a series of excellent illustrations. The three illustrations of the operation of reefing the capsule for recurrent dislocations of the shoulder-joint are not so valuable and will mislead the surgeon who is led to try this operation. They show an impossible exposure of capsule, ignore the important overlying rotator muscles, and show the external rotators attaching to the humerus below the surgical neck, whereas the capsule attaches to the anatomical neck above the tuberosities, which are consequently below and outside the joint. To limit the phases of trauma to be discussed is not a simple task, especially with reference to its late and indirect effects. The author has aimed to present information necessary for the diagnosis and treatment of all the usual and most of the unusual effects of accident and injury. A chapter is given to the eye and ear examinations of railway and other employees and another to medicolegal phases.

T. T. T.

PROGRESS

<div style="text-align:center">OF</div>

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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A New Instrument for Percussion and Auscultation.—In the continual struggle for accuracy in methods of physical diagnosis, TORNAI (*Wien. klin. Wchnschr.*, 1916, xxix, 1625) describes an instrument which he considers a distinct advance in the field of auscultation and percussion. It is a modification of an earlier apparatus which he described in connection with "phonoscopic percussion" in 1912, and which he called at that time the "phonoscope." The new instrument is called the "novoscope," and consists essentially of a single-stemmed stethoscope bell or chest piece connected by a short piece of stethoscope tubing to a metal Y tube, the two arms of the Y being connected with the ears by rubber tubing and vulcanite olives, or by tubing and the ordinary metal stethoscope ear pieces. The metal Y is connected to a metal head piece, such as is used with head mirrors, by means of an aluminum rod, which has a joint in its center permitting movement of the distal half of the rod upward through 180° in the vertical plane. The connection of the rod to the head band is made by a ball and socket joint which can be locked by a thumbscrew. With the head piece adjusted and the ear pieces in position, locking the ball and socket joint with the rod extended in front of the examiner's head permits him to percuss, with the stethoscope bell just above the percussing fingers, and the examiner listens to the percussion sounds through the medium of the stethoscope. Loosening of the ball and socket joint on the head piece converts the instrument into an easily usable stethoscope for auscultation. The writer contends that percussion tones are heard much better by this method, which enables

finer distinctions to be made in the pitch and quality of the percussion notes, so that greater accuracy is secured in the percussion of the chest and its contents. He states that very light percussion strokes must be used—preferably the so-called "threshold percussion"—and the patient examined in a very quiet room. The results obtained by this method of percussion in his hands are exceedingly accurate. The instrument is small and can be folded to carry in the pocket, and is so simple in design that any clever mechanic can construct one in a very short time.

Diminished Blood Platelets and Marrow Insufficiency.—MINOT (*Arch. Int. Med.*, 1917, xix, No. 6, p. 1062) discusses at length the findings in a series of cases of purpura hemorrhagica and aplastic anemia. The two conditions are often confused, and in most text-books no differential diagnosis between the two conditions is mentioned. There is also often much confusion between the chronic types of purpura hemorrhagica and hemophilia, this confusion usually arising from incomplete studies of the blood in these cases. Minot's conclusions were derived from the literature (of which he presents an extensive bibliography) and from the study of some 25 cases in the purpura hemorrhagica and aplastic anemia groups. Purpura hemorrhagica is a condition in which there is bleeding from one or more mucous membranes, often purpuric skin lesions, associated with diminished blood platelets, a delayed bleeding time, and a soft non-retractile blood clot. The coagulation time is normal or slightly delayed, rarely much delayed. The condition is more usually secondary to some recognized disease, as diphtheria or tuberculosis, and is also to be considered secondary when it appears as a symptom accompanying aplastic anemia, leukemia, bone-marrow tumors, pernicious or splenic anemia, etc. When no recognized cause can be found for its presence it is then spoken of as a disease entity—purpura hemorrhagica or Werlhof's disease. Idiopathic purpura hemorrhagica may be a disease that is acute, subacute, chronic or of an intermittent nature. A congenital and hereditary type exists. Acute aplastic anemia is a disease of unknown etiology which runs a progressively downward, fatal course of three to six weeks' duration. It occurs usually in patients between fifteen and thirty years of age. Fever frequently occurs, and there is no evidence of increased blood destruction as in pernicious anemia. It seems that whatever the cause of the disease may be its action is to inhibit the activity of the blood forming elements in the bone marrow, for at autopsy the marrow is found to be completely fatty. Near the termination of pernicious anemia, and in the course of certain infections, as sepsis, malignant endocarditis, typhoid fever, diphtheria, miliary tuberculosis, etc., aplasia or exhaustion of marrow may occur. In such instances we speak of a secondary aplastic anemia, the only difference between this form and the idiopathic aplastic anemia being that in the first type we recognize a source for the toxin formation and in the second we do not. In aplastic anemia the blood picture shows no evidence, or very little, of regeneration of the red cells, platelets or polynuclear leukocytes. The red cells may be very low in number (often 500,000 before death), and yet the color index averages 0.8 or slightly higher, and there is little or no variation in shape and very little variation in size. Polychromatophilia, stippling, blasts,

reticulated red cells and Howell-Jolly bodies are absent or rare. If the color index is high, and there is an occasional and unduly large and especially an oval shaped erythrocyte found, with all the other characteristics of an aplastic anemia, the suspicion that the case was one in which an aplasia of the bone marrow had developed in the course of pernicious anemia is warranted. The platelets in aplastic anemia are markedly diminished in number, often nearly absent, and they vary in size in different cases. The white cells are diminished in number, more so as the disease progresses. The leukopenia consists in an absolute diminution in the number of polynuclear cells and usually disappearance of the eosinophiles, with thus a relative but not an absolute increase in the lymphocytes, the percentage of lymphocytes averaging 73 per cent. These cells are of the normal type. There is usually a "shift to the left" (Arneth) in the polynuclear types contrasted with the frequent "right handed shift" pointed out in pernicious anemia by Briggs. The only distinctive feature of the blood picture in purpura hemorrhagica is the marked decrease in the number of blood platelets. The blood picture in this disease is therefore one consistent with a bone marrow which is incapable of forming platelets, but competent to a greater or less degree to produce polynuclears and red cells. The anemia in these cases is due to the hemorrhages and not apparently to any lack of formation or increased destruction of red cells. The red cells then are of the type usually found in an acute or chronic posthemorrhagic anemia—variation in size evident in shape, slight, some achromia occurs, and the color index is usually lowered. Polychromatophilia and stippling occur, occasionally a few normoblasts, and rarely a Howel-Jolly body. Reticulated red cells are increased when definite anemia is present. The white cells are usually increased, usually about 12,000 and sometimes higher, with an increased percentage of polynuclear elements in the higher, and often in the lower counts. There seems to be a slight "left-handed shift" (Arneth) in the types of polynuclears. The platelets are diminished often as low as 1000. The normal count is 225,000 to 325,000. When the platelets are decreased below 60,000 hemorrhages tend to occur. This decrease in platelets is in marked contrast to the increase, frequently to 1,000,000, seen in ordinary posthemorrhagic anemias in which the picture is one of active bone marrow regeneration of all three of the formed elements. The platelets usually vary greatly in size being both abnormally small, and abnormally large. There are also cases which present blood pictures intermediate between these two groups, and which suggest that in them some agent is at work interfering unequally with the production of the formed elements. Such cases are those of purpura hemorrhagica which show no increased white count or a leukopenia, or a normal or slightly increased white count with a moderate increase in lymphocytes (50 per cent.). Other cases show chronic anemia without evidence of blood destruction and little hemorrhage, red cells suggestive of poor erythrocytic activity of the marrow, leukopenia with slight relative and absolute decrease of the polynuclears, and somewhat diminished platelet counts. These cases suggest a stage midway between purpura hemorrhagica and aplastic anemia. There are also cases in which the picture is that of an aplastic anemia, and yet in which the red cells show evidence of regeneration and the leukopenia and decrease in platelet count are not marked. These intermediate

cases seem related to the more clearly cut disease known as idiopathic purpura hemorrhagica because in common with it the nature of the disease process is unknown, the most marked symptom is purpura, and the most striking blood finding is the diminution in blood platelets. The data suggest that all these conditions with diminished platelets and purpura are similar, whether the marrow only is involved or whether there is increased platelet destruction in the plasma. The stimulation of the marrow in these cases offers the greatest hope in their treatment, and this is best done by transfusion. The study of the absolute and relative numbers of the polynuclears, the reticulated red cells and the platelets is the most satisfactory way of determining bone marrow activity. Needless to say, in asplastic anemia there is no evidence of bone marrow activity following transfusion, but in some cases of purpura hemorrhagica all of the formed elements may be favorably affected after transfusion, and in other cases only the red cells and poly-nuclears. In the intermediate cases the beneficial effects of transfusion upon the red and white cell production may be very slight, suggesting a partial aplasia of these marrow elements. The studies of the bone marrow in idiopathic purpura hemorrhagica have been rather few, and Minot reports an increase of the number of megakaryocytes in the marrow of a boy, aged fourteen years, who died from idiopathic purpura. The platelets may be reduced in the peripheral blood by destruction of the megakaryocytes of the bone marrow, by some toxin which inhibits the formation of platelets by the megakaryocytes or by destruc-tion of the platelets in the peripheral circulation. It may possibly be that rapid destruction of platelets in the peripheral circulation causes in some cases, a depression of the whole marrow. In the aplastic anemias the reduction of platelets is due to diminution of the mega-karyocytes just as the decreased red count is due to diminution in the red and white cell elements of the marrow. In certain of these cases presenting the blood picture of aplastic anemia the marrow may show areas of aplasia and areas of hyperplasia. These cases are really ones of incomplete aplasia and many cases terminating as complete aplasias show early in their courses a few regenerative red cells, produced by foci of still active marrow attempting to repair the destructive process. In the symptomatic cases of purpura hemorrhagica appearing in leukemia or tumor infiltrations of the marrow the megakaryocytes have been displaced by the new cells, so that they are decreased in number. In aplastic anemia it is reasonable to assume that some factor attacks the whole marrow, the red cell elements being inolved first and the platelets later as evidenced by the hemorrhage appearing after the anemia, while in purpura hemorrhagica the platelets are attacked first so that hemorrhages appear before the anemia which is largely referable to the loss of blood. In the cases intermediate between purpura hemorrhagica and aplastic anemia the "toxin" is probably such that, besides injuring the activity of the megakaryocytes, it impairs the function of either or both of the red and white cell elements of the marrow. In chronic diseases where depression of the marrow exists, there seems to be no "toxin" at work, but possibly a congenital peculiarity of the blood forming elements of the marrow, or a super-normal sensitivity to some toxin that ordinarily produces no such effect. It is also conceivable that disease of some other organ such as

the spleen may cause depression or inactivity of the bone marrow, just as disease of one of the glands of internal secretion may depress one of the others. The author then discusses the differential diagnosis of purpura hemorrhagica and aplastic anemia, pointing out that drug purpuras Henoch's purpura and Schoenlein's disease are not true purpura hemorrhagica. Purpura hemorrhagica and aplastic anemia must not be confused with hemophilia, the non-leukemic phase of leukemia, bone marrow tumors, pernicious anemia and splenic anemia. The distinguishing characteristics of hemophilia are the normal platelet count, blood clot and bleeding time, with the greatly delayed coagulation time; of the non-leukemic phase of leukemia, the picture of active regeneration of the red cells and polynuclears, the presence of abnormal forms of lymphocytes, and swelling of the lymph nodes; of bone marrow tumors, the history, physical examination, roentgen-ray findings (Bruce Jones protein in the urine in myeloma) and presence of abnormal cells, plasma cells or tumor cells should they occur in the peripheral blood; of pernicious anemia after aplasia of the marrow has occurred, the history of remissions, sore tongue and spinal involvement, color of the skin, and a high color index of the red cells with the presence of occasional large and abnormally shaped red cells; of splenic anemia, rather marked enlargement of spleen and later of the liver, though this disease is often difficult to distinguish from purpura hemorrhagica. The author gives a short classification of the types of purpura hemorrhagica and aplastic anemia and suggests that, instead of calling a group of disease conditions "purpura hemorrhagica," we use more specific terms and referred to cases of "insufficiency of the marrow with especial involvement of the platelets or other formed elements in varying degrees."

SURGERY

UNDER THE CHARGE OF

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Treatment of Gunshot Wounds of the Abdomen, with a Summary of 500 Cases seen in an Advanced Casualty Clearing Station.— LOCKWOOD, KENNEDY and MACFIE (*British Med. Jour.*, March 10, 1917, p. 317) say that the earlier the patient could be operated on the better were the results. As late as twenty hours after being wounded, operation was considered the best course, and their results justified them. Judgment in cases seen after twenty to thirty hours presented much greater difficulties; there was always the danger of increasing the damage by manipulation during the operation. If general plastic peritonitis had developed, interference was not only valueless but dangerous; they were content to insert a pelvic drain, or, if a fecal fistula was found, to mop it out carefully and drain.

A few cases were operated on after thirty hours, but usually to drain a fecal collection. Autopsy was performed in some 80 per cent. of the cases which ended fatally without operation having been attempted; hemorrhage was found as the commonest cause of death. Shock accounted for most of the deaths within the first twenty-four hours after operation. General peritonitis was rare in cases operated on not later than twelve hours after being wounded, but later than that it was present in about 50 per cent. of deaths. Gas gangrene, especially of the posterior abdominal wall, was the cause of death in at least 30 per cent. of the cases. After nephrectomy and splenectomy death from embolism and infarct occurred in a small percentage of cases. In about 8 per cent. of cases operated on wounds of other parts of the body caused death. Of the 500 cases 356 were operated on and 144 were not operated on. The following conclusions were drawn: wounds of the large vessels to the liver, kidney, and spleen are fatal before they can come to operation. Wounds involving the pancreas are seldom seen on the operating table, by reason, perhaps, of the contiguity of the organ to large vessels; only one case was seen. In that the foreign body was lodged in the tail of the pancreas. Anteroposterior wounds, especially in the epigastrium, are least dangerous, and wounds from side to side, especially low down, are dangerous. Wounds of solid viscera are not so dangerous as those of hollow viscera. Cases that come to operation with a herniated loop of bowel exposed do badly, especially if much bowel is lying exposed; the same is true when the stomach is partially herniated. Wounds of the stomach, colon and especially the small intestine, require exploration, but in a posterior wound involving the colon the greatest care should be taken not to convert a retroperitoneal condition into an intraperitoneal one. Wounds of the liver and kidney should be carefully determined as such only, and then treated expectantly, doing no more than exploring and cleaning up the track, and not that if probably a through and through wound produced by an undistorted rifle bullet or shrapnel ball. Avoid resection. End-to-end anastomosis is preferable to lateral when resection is essential. Wounds of the diaphragm are not necessarily fatal, nor even to be greatly feared. Careful repair gives excellent results. Multiple drainage tubes are rarely necessary, and always to be avoided if possible. Abdominal lavage is a dangerous practice. Never leave free, unprotected gauze in the abdomen. Paul's tube should be relegated to the museum, except in very rare cases. Speed in operating is essential, not only for the benefit of the patient, but because of the demands of scores of less vitally wounded me requiring attention during an active offensive. Resection for fecal fistula is better done late when the patient is in England.

Direct Transfusion of Blood, with a Description of a Simple Method.— FULLERTON and DREYER (*Lancet*, May 12, 1917, p. 715) say that treatment by direct transfusion of blood has attracted much attention of late during the course of the war, since benefit has been derived from it in many cases of hemorrhage and in certain cases of anemia secondary to sepsis. Lives have been saved when all other methods of resuscitation have failed. In many cases the effect has been immediate and dramatic. They have seen patients who were blanched and shocked and with pulse hardly perceptible brought back to life in a most astonishing way.

At the same time they do not recommend its indiscriminate use, and they have only resorted to it in cases which they considered desperate. Transfusion is effected from a small artery to a suitable vein. The apparatus used consists of two glass or silver cannulæ connected by a short length (about 7 inches) of India-rubber tubing, the whole being coated within and without by a thin layer of wax made by mixing hard and soft paraffin, in about equal parts. They use thin-walled, transparent, India-rubber tubing which will stand heat and which will allow pulsations to be easily felt during the operation. The cannulæ they have found most useful are made of silver with a bulbous end so as to ensure their retention in the vessels without the necessity of tying or holding them in. Glass cannulæ of similar size and shape may be used. The ends of these are bevelled by grinding on stone or brick to facilitate introduction. They have the advantage of being easily improvised in any ordinary clinical laboratory, but it is difficult to make a bulb of suitable size to fit tightly into the vessels, and they, therefore, require to be tied in or held—a most tiresome process. The dimensions of the cannulæ are as follows: Arterial cannula: length, 4 cm.; external diameter at point, 3 mm. The operation is done under local anesthesia. The radial artery of the donor was found most suitable, and one of the veins of the elbow or the internal saphenous of the recipient. When the two vessels to be employed are exposed they are ligated at their distal ends and a light bull dog forceps is placed on the proximal end of each. A V-shaped incision is then made with sharp scissors into each vessel. The introduction of the cannula is facilitated by making the incision in the vessel close to the ligature and seizing the flap thus made at its extremity with a fine forceps. The opening is thus made to gape. An analysis of the 16 cases transfused by this method shows that 1 received no blood owing to an undetected obliteration of the receiving vein. In 3 the patients appeared beyond hope of recovery and transfusion was only undertaken as a last resort. Of the other 12 in which improvement might have been anticipated, 4 made rapid and very satisfactory progress, which is attributed, without hesitation, to transfusion. In another case the recovery was not attributed to the transfusion. The remaining 7 cases died although hopes of their recovery were entertained. The fact that improvement took place in most of the cases that died encourages the belief that under similar circumstances in future transfusion might just tide the patient over a critical period and allow time and opportunity for further surgical treatment. Three cases transfused by this method by two other surgeons gave excellent recoveries.

Influence of the Venous Collateral Circulation of the Kidney on Hydronephrosis.—BARNEY (*Ann. Surg.*, 1917, lxv, 597) says that one of the earliest effects of sudden and complete obstruction of the ureter is the production of an intense hyperemia and edema of the kidney. The intrarenal pressure slowly rises by damming back the urine which is being formed, and this in turn produces a slow but constant dilatation of the uriniferous tubules. This compresses the venous capillaries, especially those in the cortex, and serves to perpetuate the changes already started. At first only the venous capillaries are affected, but later the artificial circulation also becomes involved. If then the venous apparatus both in the fat capsule and on

the surface of the kidney is well developed, as it usually is, the anastomoses described by Tuffier and Lejars will take up the work for which they were intended and carry on, more or less perfectly, the venous circulation of the kidney. If, on the other hand, as may occasionally happen, this accessory, venous circulation develops either not at all or but slowly, the secretion of urine soon ceases, hydronephrosis will not develop, and atrophy of the kidney will take place. From an experimental study on seven dogs, he concludes that: Sudden, complete and permanent obstruction of one ureter produces hydronephrosis in animals in the vast majority of cases, but atrophy of the kidney may develop in rare cases. When hydronephrosis occurs the venous collaterals of the kidney are well developed; when atrophy of the kidney takes place it is due to a lack of development of these collaterals. Atrophy of the kidney may be produced experimentally, by simultaneous ligature of the ureter and veins which maintain the collateral venous circulation of the kidney. When the obstruction to the ureter is partial or intermittent the hydronephrosis is of greater size than when the obstruction is complete, sudden and permanent, for in the latter event, urinary secretion ceases before the venous collateral circulation has time to develop.

Results of Surgical Treatment of Gastric Ulcer.—BALFOUR (*Surg., Gynec. and Obst.*, 1917, xxiv, 731) based the following conclusions on 677 gastric ulcers operatively demonstrated in the Mayo Clinic during the past ten years: For ulcers of the pylorus, posterior gastro-enterostomy is the operation of choice in the poor surgical risk, for although pylorectomy is followed by better results, the operative mortality is distinctly higher. The cautery is a useful adjunct in selected cases. For ulcers on the lesser curvature, cautery by the method described in a previous paper and gastro-enterostomy is the operation of choice. Local excision alone of such ulcers is inadequate, 32 per cent. of patients so operated on ultimately requiring further operative treatment, viz., gastro-enterostomy. Sleeve or segmental resection, especially in large, high ulcers and hour-glass contraction in suitable cases is not only a relatively safe operation but has been followed by good results. The lowest operative mortality in the more common operations was associated with cautery and posterior gastro-enterostomy. Ulcers on the posterior wall are associated with the highest operative risk, while those at the pylorus are of least risk.

Growth of Free Bone Transplants; An Experimental Study.— TODYO (*Surg., Gynec. and Obst.*, 1917, xxiv, 701) says that the bone with its periosteum, if it is transplanted in the same body under favorable conditions, continues to live. While among the various components of the transplanted bone the bone cells and the marrow have changed their ability to take the nuclear stain at the end of the third week after the transplantation, the periosteum, the subperiosteal tissue, the epiphyseal cartilage and the epiphyseal line, give distinct evidences of life. Among the various components of the transplanted bone the periosteum and the subperiosteal tissue have not only lived throughout every period of the examination but have executed an active formation of new bone. Most of the epiphyseal cartilage and epiphyseal line have

lived throughout every period of examination, as has the periosteum, and they have, moreover, carried on an active proliferation and ossification. Yet they are irregular, losing their physiological relationships. The bone cells and the marrow have lost or changed the staining power of the neucleus in a short time after the transplantation but the physiological or nearly physiological appearance returns after a certain time, being replaced by the resistant components of the transplants. The aperiosteal transplant grows and regenerates by the proliferation of cells in the subperiosteal layer. But in each case the new growth of bone is not so active as in the transplants with periosteum. The aperiosteal transplant acquires a new periosteum. The aim of the bone transplantation can be reached without the periosteum and marrow of the recipient. As to the continued life of the transplanted bone, however, Todyo cannot give a definite opinion at this time. Transplanted bone grows; the increase in thickness is marked, although the length increases but little when transplanted with the epiphyseal line.

THERAPEUTICS

UNDER THE CHARGE OF

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The Intramuscular versus the Intrathecal Route in the Treatment of Tetanus by Injection of Antitoxin.—BRUCE (*Lancet*, 1917, cxcii, 680) relates experiments on monkeys undertaken to establish whether the intramuscular or the intrathecal administration of tetanus antitoxin has greater protective forms against tetanus antitoxin. Although the experiments are at present few in number Bruce believes that the results are distinctly in favor of the greater efficacy of the intrathecal as against the intramuscular method.

A Report of Twenty-five Cases of Tetanus.—DEAN (*Lancet*, 1917, cxcii, 673) reviews 25 cases of tetanus treated by tetanus antitoxin administered by intravenous, intrathecal, intramuscular and subcutaneous injection. Of 5 mild cases treated by intramuscular and subcutaneous injections of serum, 5 recovered. Of 14 cases treated chiefly by intravenous injections; thirteen recovered. Of 5 cases treated by intraspinal with or without other injections 3 recovered. Dean says if the signs are well localized and not spreading rapidly, intramuscular injections afford an adequate method of treatment. In severe cases, and in those in which signs are generalized, an intravenous injection of 30,000 units under deep chloroform anesthesia should be given. After such injection the further progress of the disease is usually arrested and definite improvement may be expected two to seven days later. The author believes that the essential principle of serum treatment is

to give a very large dose of antitoxin at the earliest possible moment. This object can be most easily attained by the intravenous route. Dean believes that the danger attributed to intravenous injection of tetanus antitoxin has been exaggerated. In 4 cases serum treatment was confined to a single intravenous dose of 30,000 units. In 3 other cases no serum was given subsequent to the intravenous injection. In these 7 cases recovery was as rapid as in 6 other cases in which subsequent injections were given. The serum of patients was shown to contain free antitoxin at various intervals up to thirty-nine days after an intravenous injection of 30,000 units. Dean emphasizes particularly the beneficial effects derived from prophylactic injections of the antitoxin. He believes it probable that almost all, if not all of the 25 cases here reported had received prophylactic injections in France. In 3 of the 25 cases the disease ran an extremely short and mild course. These were the only 3 patients who had received a prophylactic injection after their arrival in England. The author states that if every wounded soldier, irrespective of the size or condition of the wound, was given a prophylactic injection on his arrival in England there would in all probability be a still further reduction in the number and severity of cases of tetanus. One result of prophylactic injection is to prolong enormously the incubation period, with the result that tetanus may occur after the wounds have completely healed. Therefore it is very important to watch carefully for the earliest signs and sypmtoms of the disease.

The Intravenous Injection of Arsenobenzol in Concentrated Solution. —FAIRE and MARSIA (*Presse Médicale*, 1917, xxii, 221) say that they have given 3150 injections of neosalvarsan or novarsenobenzol Billon, dissolved in an amount of water never exceeding 2 c.c. They found that novarsenobenzol dissolved very quickly by the addition of the water to the drug contained in the ampoule and gently shaking it until completely dissolved. Neosalvarsan did not dissolve so readily and they advise that care should be taken to distribute the neosalvarsan in a thin layer over the lateral walls of the ampoule by tilting the ampoule and gently rotating it. This simple manipulation prevents the formation of a semisolid mass at the bottom of the ampoule and allows the drug to go easily into solution. Distilled water was usually used to make the solution, but when it was not available, boiled filtered water was used without producing any untoward reaction. The authors state that the concentrated solution is perfectly well borne and they have not observed any vein irritation produced by the injections. Inflammatory induration has occurred due to leakage from the vessel into the surrounding cellular tissues but is not more marked than that occurring from much more dilute solutions. General reactions were usually not observed; in a few instances very mild general reactions followed the injections.

The Intramuscular or Subcutaneous Injection of Neosalvarsan.— HARRISON, WHITE and MILLS (*British Med. Jour.*, 1917, 2940, 569) write concerning the comparative effects obtained by treating two parallel series of cases of syphilis by intravenous injection of salvarsan, including various substitutes for salvarsan, and by the deep subcutaneous or intramuscular injection of neosalvarsan as its substitutes.

The substitutes used by the authors were arsenobenzol, kharsivan and arsenobillon, and it was found by them that these substitutes had practically the same therapeutic effect as salvarsan. The same corresponding results were also obtained by using novarsenobenzol or novarsenobillon in place of neosalvarsan. The authors state that the intramuscular or subcutaneous injection of neosalvarsan and its substitutes was found to be superior in immediate therapeutic effect to that of the intravenous injections of salvarsan and its substitutes. Spirochetes disappear from syphilitic lesions just as rapidly after the first intramuscular as after the first intravenous injection, and the Wassermann reaction is more quickly influenced. The only practical disadvantage is the discomfort at the site of the injection caused by the deep subcutaneous or intramuscular use of neosalvarsan. This can be largely avoided by dissolving the dose of neosalvarsan in 1 c.c. of a 4 per cent. stovaine solution and making the amount up to 2 c.c. by creocamph cream which melts at 15° C. In a footnote the authors state that the creocamph cream was later replaced by camphophenique with equally good results and this has proven to be the most comfortable method of injection up to the present. The general reaction which follows an intramuscular injection is much less than after an intravenous. The authors believe that the tonic effect of such intramuscular injections is much greater than when the remedy is administered intravenously.

A **Comparison of the Subcutaneous with the Intravenous and Intrathecal Administration of Tetanus Antitoxin in Experimental Tetanus.**—GOLLA (*Lancet*, 1917, cxcii, 686) says that the results obtained by him in animal experiments show the undoubted superiority of the intravenous and intrathecal methods of administering tetanus antitoxin over the subcutaneous. He believes that tetanus antitoxin injected subcutaneously is absorbed too slowly to be available quickly enough to combat the disease.

The Treatment of Syphilis of the Central Nervous System.—HALLER (*Arch. Int. Med.*, 1917, xix, 997) in his article deals with the comparative results obtained in the treatment of cerebrospinal syphilis by mercurialized and salvarsanized serum. He says that a comparison of the efficacy of the two serums in relieving symptoms and in causing objective changes in signs and in the laboratory findings offers more difficulties than are encountered in a comparison of the reactions from treatment. Tables are given in the article showing the comparative effects on the clinical symptoms and laboratory findings. In his conclusions he states that: "The irritating effect in the spinal canal of serum to which mercuric chlorid has been added in the dose of 0.001 gm. is greater than that of 20 c.c. of salvarsanized serum separated from blood drawn thirty minutes after a dose of 0.6 gm. of salvarsan. The average effect on the laboratory findings in the spinal fluid from one dose of mercurialized serum is greater than from one dose of salvarsanized serum. Unpleasant symptoms are more common following intraspinal mercurialized serum than following salvarsanized serum. The greater irritation of the meninges from mercurialized serum prevents as rapid repetition of the dosage as is possible with salvarsanized serum."

Consequently the results at the end of a year of treatment, if each serum were used to the greatest extent consistent with safety, probably would not show such a discrepancy against salvarsanized serum because of the larger number of doses which could be given. He also states that cases of general paresis, meningitis and cerebrospinal syphilis stand intraspinal treatment with mercurialized serum better than do cases of tabes dorsalis. It is particularly in cases of active syphilis of the meninges that the mercurialized serum is useful. Mercurialized serum has an advantage over salvarsanized serum in case of preparation and in its keeping qualities. For these reasons it can be used under clinical conditions in which the use of salvarsanized serum is impossible, or at least very much more difficult. A comparison of the ultimate results obtained with the individual cases in the two groups is impracticable because of the difference in the total amount of treatment which has been given to the two groups, and also because of the small interval of time which has elapsed since treatment was discontinued, or because many of the group treated with mercurialized serum are still under treatment.

The Effect of Ingestion of Coffee, Tea and Caffein on the Excretion of Uric Acid in Man.—MENDEL and WARDELL (*Jour. Am. Med. Assn.*, 1917, lxviii, 1815) found that the addition of a strong coffee infusion to a purin-free diet causes a marked increase in the excretion of uric acid. The addition of Kaffee Hag—a decaffeinated coffee product—to a purin-free diet does not cause any increase in the excretion of uric acid. If, however, caffein is added to the Kaffee Hag the excretion of uric acid is decidedly increased, as in the case of coffee. The effect of adding tea to a purin-free diet is similar to that obtained by adding coffee to the same diet. The increase in excretion of uric acid after adding coffee, tea or caffein to a purin-free diet seems to be proportional to the quantity of caffein ingested. The increase in the amount of uric acid excreted under these conditions is equal to the quantity of uric acid which would be obtained by the demethylation and subsequent oxidation of from 10 to 15 per cent. of the ingested caffein. The results of this series of investigations suggest interesting possibilities for further research. Additional experiments should be performed to determine whether or not the increase of uric acid excretion is always directly proportional to the quantity of caffein ingested. At the same time, the purin-base content of the urine should be determined in order to learn whether the increase in uric acid excretion is due directly to the conversion of caffein itself into uric acid or to an indirect stimulation of purin metabolism. The whole question is further complicated by the presence of tannin derivatives in all the beverages under discussion. Earlier observations of a number of authors indicate that the ingestion of tannic acid and tannin causes a decrease in uric acid excretion. On the other hand, others fail to show any such results. This phase of the problem could be settled by detannated coffee being used in place of a decaffeinated product. Finally, it would doubtless prove interesting to perform similar series of experiments with dogs and rabbits in order to study the effect of caffein ingestion on the excretion of uric acid and of allantoin in species in which uric acid is not the prominent normal end-product of purin metabolism.

PEDIATRICS

UNDER THE CHARGE OF

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Enlargement of the Thymus Treated by the Roentgen Ray.—
FRIEDLAENDER (*Am. Jour. Dis. Children*, July, 1917, xiv, No. 1) empha-
sizes three facts: (1) The condition is much commoner than is ordinarily
supposed. (2) The diagnosis can be made definitely by means of simple
physical examination and the roentgen ray. (3) In the roentgen ray
is possessed a therapeutic agent which, in and of itself, will effect a cure
in a majority of cases. As an illustration of the first fact he cites the
experience of Dr. J. E. Benjamin, who saw 225 new cases in a year's
service at the University of Cincinnati. Congenital syphilis, famial
tendency, and association of hypertrophic pyloric stenosis are men-
tioned as possible etiological factors in this condition in which no definite
etiology has been determined. The principal symptoms are dyspnea,
suffocative attacks with cyanosis, and stridor. The physical signs are
a bulging mass in the jugulum, enlarged area of thymus dulness on
percussion, better elicited by using very light percussion. The roentgen
ray is of great use in diagnosis if the plates are made with the patient
lying squarely. In this series 100 cases were treated with the roentgen
ray. Four deaths occurred. The remainder of the cases were either
greatly benefited or apparently cured. In the most instances improve-
ment was noticed from twenty-four to forty-eight hours after the first
treatment.

**Relation of Mosquitoes and Flies to the Epidemiology of Acute
Poliomyelitis.**—NOGUCHI and KUDO (*Jour. Exper. Med.*, July, 1917,
xxvi, No. 1), from the Laboratories of the Rockefeller Institute of
Medical Research, state that Culex pipiens from sewer waters of Jersey
City were raised in water contaminated with poliomyelitic virus. No
infection was caused when large numbers of these mosquitoes were
allowed to bite monkeys. Full grown Culex pipiens were fed on infected
poliomyelitic monkeys during different stages of the disease. These
did not transmit the infection when large numbers were allowed to bite
normal monkeys. The injection of horse serum into the intrathecal
space to cause a previous disturbance of the meninges did not alter the
result. The offspring of mosquitoes, which were either raised in the
infected tanks or fed on infected monkeys, were found to be entirely
harmless when allowed to feed in large quantities on normal monkeys.
There was no hereditary transmission of the virus from one generation
to another. A filtrate of the emulsion of adult flies and pupæ of the com-
mon blue-bottle fly and house fly, which were reared in the laboratory
on slices, emulsion, or filtrate of monkey brain containing poliomyelitic
virus, showed no trace of the virus. The intracerebral injection of the
filtrate produced no poliomyelitic infection in normal monkeys. The
authors point out that the experiments of Rosenau and Brues in 1912

were of a different character. They allowed stable flies to feed first on infected monkeys and immediately afterward on a well monkey. Transmission in these test was mechanical and not in the sense of an intermediary host.

The Age and Seasonal Incidence and Communicability of Acute Poliomyelitis.—HERRMAN (*Jour. Am. Med. Assn.*, July 21, 1917, lxix, No. 3) has studied the statistical results of the epidemic of 1916 in New York City. This is the largest epidemic of the disease on record. He shows that the crippling resulting from poliomyelitis is less than from the other communicable diseases and heart disease. A child with a partially paralyzed limb is less handicapped in the struggle for existence than one with defective hearing or a diseased heart. The other communicable diseases are more common and causes more deaths. Susceptibility is more marked in infants and young children. Young infants are less frequently attacked because less exposed to infection. A large proportion of patients under five years of age do not indicate a mild epidemic. The same increase of susceptibility of the central nervous system is seen in the age incidence of tuberculous meningitis. In temperate climates epidemic occur during the summer months, but sporadic cases occur throughout the year. In Scandinavia, epidemics have extended into the winter months. Meteorological conditions do not play the most important role in the spread of the disease. Seasonal changes in the power of the nasopharyngeal mucous membrane to neutralize or inactivate the virus of poliomyelitis may account for the increased susceptibility. Patients who have had poliomyelitis seem to be more susceptible to ordinary nasopharyngeal infections. The susceptibility of children under thirteen years of age to poliomyelitis is much less than to the other communicable diseases of childhood. It is present in only about 2 per cent. The susceptibility is about fifty times as great, to whooping-cough about thirty-five times, and to scarlet fever and to diphtheria about ten times. Children who are susceptible to poliomyelitis are not necessarily more susceptible to the other communicable diseases. There exists a distinct individual predisposition. Because a majority of the susceptible children have immunized by having had the disease or by having been exposed to it, no large epidemic is expected in New York City for some years. A future epidemic could be controlled if we had a method of detecting the 2 per cent. of susceptible children and could immunize them with convalescent serum.

Pertussis Vaccine.—SHAW (*Am. Jour. Obst.*, July, 1917, lxxvi, No. 475) says that "statistics prove that in young children whooping-cough is the most fatal of the group of so-called infectious diseases of childhood. Fully 80 per cent. of the deaths from whooping-cough in New York State during the five year period, 1910 to 1914 were of infants under two years of age and ninety-six of the whooping-cough deaths were children under five years of age. The importance of controlling and preventing a disease which has such a high mortality in early life and such a long and often protracted course, leaving the child debilitated and susceptible to bronchopneumonia, tuberculosis, and diarrheal disease, cannot be too strongly emphasized. The most rational and important step in the control of whooping-cough is the prevention of the

disease itself. The very great importance of the early recognition and prompt reporting to the health authorities of whooping-cough should be realized by the general public and the medical profession. Every case should be regarded as suspicious until its real nature is ascertained, and while in doubt the child should not be allowed to associate with children. Penalties prescribed by the Sanitary Code for failure to report cases of whooping-cough should be enforced just as rigidly as in the case of infantile paralysis, diphtheria, and smallpox. Infected children should be isolated from other children, and in the street should wear a distinguishing mark, such as an arm band with the words 'whooping-cough' in large letters. The sputum and vomitus should be treated in the same manner as in tuberculous affections. The fact that there are 999 alleged 'sure cures' for whooping-cough is proof that we have not yet found a medical remedy of much value. The discovery of the Bordet-Gengou organism has opened the way for a more rational and scientific mode of treatment. Pertussis vaccines are prepared by several commercial houses, by the New York City Department of Health, and in the laboratories of the State Department of Health. Those prepared and recommended by the commercial houses are polyvalent, that is they are mixtures of vaccines, not only containing the Bordet-Gengou bacillus, but containing the influenza bacillus, streptococci, staphylococci, etc. The vaccines prepared by the New York City and State Departments of Health are pure vaccines, standardized by Wright's method from the Bordet-Gengou bacillus. In influenza Dr. Holt has shown that we may find a cough which clinically resembles that of whooping-cough, so that in these cases the pertussis vaccine would have no effect. There is also a probability that there are several types of Bordet-Gengou bacillus. These facts should be borne in mind before condemning the use of vaccines, which prove unsatisfactory in a small series of cases. Graham and Hess report experiences with pertussis vaccines which they believe warrant their further trial. At St. Margaret's House in Albany, 164 children were exposed to whooping-cough in four different epidemics and only 7 per cent. of the number developed the disease. The vaccines administered were from pure cultures prepared by the State Laboratory. In former days when whooping-cough developed in an institution, fully 50 per cent. of the inmates contracted the disease. The value of the vaccines as a prophylactic measure is undeniable, and they should be administered to every child exposed to whooping-cough. The vaccines are harmless, do not produce severe reactions, and there is no danger of anaphylaxis. The dosage used for prophylaxis at St. Margaret's House is the same as the dose for treatment, namely, five hundred million, first injection, one billion for the second, two billion for the third, giving the injections every second or third day. We have administered with good results, one billion every two days for ten days. The results of the vaccines in the treatment of cases already in the paroxysmal stage are not as striking as in prophylaxis, but the concensus of opinion of those who have employed the vaccines, is that where the proper vaccine is used there is a shortening of the paroxysmal stage, with a reduction in the number and severity of the paroxysms. A study of the use of vaccines in 212 cases of whooping-cough, in which this was the only treatment employed, shows that in 38 per cent. of the cases in which the vaccines were given after

the whoop developed, the course of the disease was shorter than the usual duration of the whooping stage, but with no effect on the number or the severity of the paroxysms. In 12 per cent. of the cases there was no improvement either in the course of the disease, its severity or the number of paroxysms."

OBSTETRICS

UNDER THE CHARGE OF

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The Bactericidal Property of Vaginal Secretion.—HARADA has studied this subject at the Obstetrical Department of the Kyoto Imperial University (AM. JOUR. MED. SC., August, 1916). He reviews the literature and describes his own methods of experimentation. He found that all of the vaginal secretion collected during his experiments was acid in reaction and that the bactericidal power of this secretion in pregnant patients increased in potency with the progress of pregnancy, reaching its climax on and after the eighth month. The bactericidal power of this vaginal secretion is strengthened with the increase in acidity. There is no other great difference in the action of this secretion upon various species of bacilli. In some cases the lactic acidity of this secretion was as much as 0.9 per cent., and although the bactericidal power of the secretion increased during pregnancy, the lactic acidity does not. The results of the writer's study show that the bactericidal power is greatly increased by the lactic acid contained in the vaginal secretion, but it was also found that the neutralized vaginal secretion possesses still some bactericidal power. There was reason to believe that certain substances are destroyed at 56° C., which are capable of killing bacteria and other substances that are only destroyed by the removal of the acid. A test was made with chemically pure lactic acid to observe its bactericidal power, and it was found to be far less than that of a vaginal secretion in a ten months' pregnancy. It was further found that although lactic acids are contained in equal quantity in vaginal secretion, the bactericidal power of the vaginal secretion is not unvarying, but increases during the course of pregnancy. There is thus abundant evidence that lactic acid is not the only agent in vaginal secretion in pregnancy capable of destroying bacteria, nor is the bactericidal power of this secretion entirely destroyed by heating to 56° C. The activity of this secretion is considerably lessened by such heating, but is not destroyed. Vaginal secretion during pregnancy may possess considerable amount of dialyzed tissue juice, and it can readily be seen that healthy tissues or blood contain several bactericidal substances. Such are termed by bacteriologists bacteriolysin or amboceptor. If amboceptor is the principal bactericidal substance it is necessary to complete its property with complement. On experiment it was found that the addition of complement fails to render the secretion effective; the bactericidal property of vaginal secretion is not

bacteriolysis, which is necessary to complete its property with comple-
ment. Metchnikoff believed that cytase was the active agent in this
phenomena, and Gruber-Futaki thought that leukin was the active
agent. Cytase is destroyed at 56° C. while leukin is not, and both
are thought to be produced by the leukocytes. As leukocytes are
abundant in vaginal secretion, it seems reasonable to believe that they
have much to do with the bactericidal property of this secretion. It
was found that frozen solution possesses stronger bactericidal power
than the unfrozen, and on further experiment it was found that the
bactericidal substance was partly decreased by heat. From his studies
the writer believes that the bactericidal property of pregnant vaginal
secretion is not greatly affected by different bacilli. This property
gradually increases during the course of pregnancy. Lactic acid in
quantity 0.9 per cent. is contained in pregnant vaginal secretion and
does not increase during the course of pregnancy. A substance which
destroys bacteria in pregnant vaginal secretion is not in the nature of
bacteriolysis, which is completed by association with complement.
This secretion owes its power to destroy bacteria to the presence of
leukin, cytase or allied substances and lactic acid. Leukin is probably
an important factor in the bactericidal activity of pregnant vaginal
secretion.

**Role of the Anteposed Uterus in the Causation of Backache and
Pelvic Symptoms.**—In examining patients in early pregnancy it is not
uncommon to find cases in which the uterus is anteflexed, strongly
anteverted and pushing downward, sometimes behind the pubis. Such
patients often complain of considerable pain, disability and backache.
HUTCHINS (*Jour. Am. Med. Assn.*, September 23, 1916) in these cases,
notes the relative position of the cervix to the symphysis pubis and
pays no attention whatever to the forward or backward position of the
fundus. The amount of posterior descent of the cervix toward the
coccyx, and not toward the outlet of the pelvis, was carefully noted.
The stability of the lower part of the broad ligament, paracervical
tissues and the uterosacral ligaments was tested by grasping the
uterus between the examining hands and moving it as far as possible
up behind the symphysis and backward toward the coccyx. By this
manipulation the backache and dragging feeling of which the patient
complained was frequently reproduced. To test the question of treat-
ment, vaginal tampons were so placed that the whole uterus was forced
well forward up back of the symphysis in the position where high sus-
pension would hold it. These tampons were allowed to remain for
forty-eight hours, the patient moving about freely and if the backache
and dragging were relieved, it was believed that suspension would
cure. In cases subjected to operation, as soon as the abdomen was
opened the intestines were gently pushed up out of the pelvis and a
careful exploration of all pelvic structures was made. The uterus was
found far down in the pelvis, although there had been no descent
toward the outlet. The fulness and congestion of the ovarian veins
is very striking in these cases, the chief tension coming on the
infundibulopelvic ligament composed of two layers of sensitive parietal
peritoneum enclosing the ovarian vessels. This stretches around the
side of the pelvic wall originating at a point posteriorly, corresponding

to the location of the sacro-iliac joints. The ovarian veins in this position become engorged up to a point where they cross the pelvic brim, but above that point they were nearly flat and empty. By slowly lifting the fundus out of the pelvis these veins were emptied, the stretched infundibulopelvic ligament relaxed. This explanation of the cause of pain when the uterus is anteposed and carried downward and backward, explains the discomfort of pregnant patients in whom the ovarian veins and all vessels of the broad ligaments are congested. While during pregnancy it would not be advisable to suspend such uteri, if the patient would take the knee-chest posture and practice deep breathing, much relief can be obtained. As pregnancy advances and the uterus unfolds and rises above the pelvis, the symptoms usually disappear.

Diagnosis and Management of Extrapelvic Conditions during Pregnancy.—ANDREWS (*Surg., Gynec. and Obst.*, December, 1916) groups these conditions as (1) injuries and accidents of all kinds; fractures; contusions; wounds, internal and external. (2) Surgical abnormalities, infections, abscesses, and mycoses of various abdominal organs, chest, neck, brain, and extremities. (3) Associated problems of the ductless glands and their metabolism during pregnancy; including the problems of serology and diagnosis as altered or vitiated by pregnancy. (1) In traumatic emergencies during pregnancy there may be an absolute indication for saving the life of the mother. Even in these cases the mode of anesthesia, method of operating, and management of the patient must be modified because of the pregnancy. When pregnant women have fractures, wounds, contusions, or other trauma the surgeon must take care to avoid shock—prolonged anesthesia, and operations which tend to produce uremia. Abortion not infrequently follows prolonged and difficult operations upon pregnant patients. What is absolutely necessary must be done, but as little as possible. (2) Non-traumatic surgical diseases must be treated on general principles. Such are appendicitis, gall-stones, gastric ulcer, tuberculous peritonitis, and allied conditions. As a rule, it is best to do no operation during pregnancy which can properly be postponed unless conditions arise which demand operation in the interests of the mother only. Each case of surgery in pregnant women is to be decided on its own merits. In the puerperal period, general principles again must be the guide of the surgeon. A dislocated kidney may often complicate pregnancy and parturition and prove a grave factor. If discovered early such a kidney may be fixed, although delivery can usually take place without operative interference. It is rarely necessary to operate upon varicose veins in the extremities during pregnancy. (3) In abnormal conditions of the ductless glands the relation existing between the generative organs and these glands must be remembered, and conditions may be found virtually caused by the pregnancy which would not otherwise be present from disease of the ductless glands only. The writer calls attentions to the danger of the use of salvarsan in pregnant women unless the arsenic which it contains is freely excreted. He adopts the rules laid down by Raeder that women expecting to be pregnant should be given a thorough physical examination. Every functional defect should be corrected before pregnancy. No operation should be per-

formed during pregnancy if it can be deferred, but any operation which will contribute to the safety of the patient should be performed although the patient be pregnant.

The Diagnosis and Management of Pregnancy in the Presence of Acute Abdominal Conditions.—DeLee (*Surg., Gynec. and Obst.,* December, 1916) draws attention to the confusion which frequently arises between ectopic pregnancy and appendicitis. The rising leukocyte count, taken every two hours, is essential in making a diagnosis. When ectopic gestation and pregnancy coexist, or ectopic gestation and salpingitis, the diagnosis may be difficult. It is necessary to make a careful vaginal examination in these cases, or otherwise pregnancy may not be suspected and pernicious nausea of pregnancy may prove fatal because confused with obstruction of the bowel. A case is described in which a woman had a gestation in the left tube, the fetus escaping into the abdomen, while the pain and rigidity, jaundice, nausea, and vomiting pointed to the gall-bladder. Ectopic gestation, so soon as a diagnosis is made, should be treated by abdominal section. Appendicitis may be confused with pyo-ureteritis and also colon bacillus infection, not uncommonly seen in pregnant women. In these cases the patients have symptoms of ureteritis, appendicitis and cholecystitis, the colon bacillus being found in the urine. In some cases jaundice develops. Acute appendicitis in pregnancy demands immediate operation, disturbing the uterus as little as possible. Should abortion be threatened at the time of operation, the uterus should first be emptied and then the abdomen opened. If the woman is at term, Cesarean section should be avoided, but the appendix should be dealt with and opium be given to prevent labor. Should the operator find that general peritonitis is present, it would be better to do hysterectomy, draining the pelvis from below. Pyosalpinx should be dealt with by removal, but cholecystitis, as a rule, does not require operation during pregnancy. In the presence of ileus, abdominal section is safest. In pyelitis, Cesarean section is not indicated for fear of infecting the birth canal. The kidney may be drained, if necessary. Uterine rupture demands section, and injury to the abdominal contents, especially the uterus, calls for immediate operation. Hernia and ruptures of various sorts are best treated by operation. In general, it is better to postpone operations on pregnant patients until after delivery.

Diagnosis and Management of Pelvic Infections Complicating Pregnancy.—Lewis (*Surg., Gynec. and Obst.,* December, 1916) believes that retroversion of the uterus during pregnancy is a grave condition, frequently resulting in abortion. When adhesions are present it may be safer to open the abdomen, separate the adhesions, and replace the dislocated uterus. Suspensory operations should be avoided during pregnancy. When pregnancy has gone beyond the fourth month it is generally safest to empty the uterus by abdominal section and to relieve the patient before symptoms connected with the bladder can develop. All cases of rupture of the uterus should be dealt with by section, but the management of the case after the abdomen is opened will depend upon the extent and location of the rupture, the amount of hemorrhage, chances of infection and somewhat on the age of the patient. When the rent in the uterus is clean cut, it is occasionally

possible to suture the uterine muscle and retain the uterus; ordinarily supravaginal amputation is indicated. Acute salpingitis in pregnancy does not demand surgical treatment. Tubal abscess, or other pelvic collections of pus should be opened through the vagina, especially during the early months of gestation. It is often impossible to distinguish between pelvic abscess and ectopic pregnancy, and frequently on opening the pelvis to empty an abscess an ectopic pregnancy is found. Ovarian tumors complicating pregnancy should be removed so soon as possible. The writer thinks that after the fifth month the uterus is so high in the abdomen and is obstructing the entrance to the pelvis so completely that removal of an ovarian tumor from the pelvis would be attended with great difficulty. The frequency of torsion of the pedicle must be remembered in these cases, which is an added reason for the early removal of the tumor.

Rupture of the Uterus, Sepsis, Operation and Recovery.—HALL (*Am. Jour. Obst.*, December, 1916) reports the case of a multipara, who had a quick and unaided labor, and, on the fourth day, a chill and temperature, which rose rapidly to 104° F. An afternoon rise and a normal morning temperature continued for some time, the patient feeling well except for slight pain or tenderness in the right lower half of the abdomen. The lochia seemed normal. The patient had no chills or sweats, good appetite and felt well, and had abundant nourishment for the child. Five weeks and three days after labor, the patient had a severe chill, the abdomen was moderately distended, not sensitive to palpation, except in the right lower quadrant; muscular rigidity was moderate on that side. No mass could be felt in the abdomen or pelvis except a large, subinvoluted uterus. Bimanual examination revealed that involution was going on well. The most natural inference was that the patient had a small ovarian cyst which had ruptured during labor. No interference at first was practised, and the patient continued to do fairly well. The temperature, however, continued to rise, and tenderness and rigidity in the right half of the abdomen were more marked than before. Six weeks after delivery the patient was growing worse. She had profuse sweats, the mass in the abdomen appeared to be three times the size it was four days previously, and more sensitive. She seemed septic, although able to nurse her child. On operation, the omentum was found adherent, and, on separating the adhesions, pus was found in front and to the right of the uterus. There had been a rupture of the uterus at the fundus, extending down to the top of the bladder. In this rent the omentum had inserted itself and was firmly adherent. The uterus was larger on one side than on the other. The omentum was severed close to the uterus and all that portion in contact with the pus-cavity removed. The appendix and Fallopian tube on that side were not involved. It was found that the ruptured surfaces in the uterus had healed spontaneously and hence the uterus was not molested. In discussion, Schwartz described a case in whom an effort was made to induce labor for contracted pelvis. Labor developed, but suddenly the uterine contractions ceased and the patient became absolutely quiet. The child was immediately extracted by the feet, and as soon as possible the abdomen was opened and a rent in the uterus repaired. A second case was that of placenta previa in which a general practitioner had applied a pack and then given ergot. The result was strong uterine contractions followed by rupture.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Transplantation of Benign Tumors.—In a detailed report on the transplantation of benign tumors in which six rat tumors were employed, Loeb and Fleischer (*Jour. Cancer Research*, 1916, i, 427) give the results of some extended experiments. The transplants were carried to the second and third generations whenever possible. Both auto- and homoiotransplantation were employed in each tumor studied. The writers, at the outset, found themselves facing difficulties which they resolved into three general questions. These may well be stated, and, with each the data resulting from their work. Primarily, their previous experience in the study of cancer led to a comparison between the growth of this tumor and the benign forms, under experimental conditions. They demonstrated that, like the malignant tumors, the benign forms can be transplanted through several generations, during which process they show both gross increase in size and microscopic evidence of proliferation. While this is true they also found that though malignant tumors increase in growth energy, possibly directly due to stimulation of tumor cells by the conditions of transplantation, benign tumors decrease in growth energy. This is apparent in the greater latent period seen in each generation of transplants over that preceding, as well as in the microscopic evidence of definitely slower proliferation. The benign tumors, whether because they are less embryonal, or contain more fibrous tissue, or are better able to vascularize themselves, have been found to be more resistant to transplantation. Also, the growth is frequently better in case a benign breast tumor is transplanted into a pregnant animal. Malignant tumors as well as embryonal tissues are found to be difficult or impossible to transplant into animals in pregnant state. This then brings up the second question, How does the growth of benign tumors compare with that of normal tissues? Craster has demonstrated that transplanted skin soon regains its equilibrium and does not undergo progressive growth. Later transplants were found to grow better than early ones, suggesting that the mere operative trauma incident to removal of the tissue for transplantation had in some way stimulated growth energy. In regard to the increased growth manifested in benign breast tumor transplants with the occurrence of pregnancy, the authors are convinced that this phenomenon is due to a specificity in reaction of this tissue similar

to that seen in the normal breast under like influences, and due to a definite chemical constitution of the tumor tissue. It is admitted, however, that in one instance the best growth in the second generation was obtained in a male rat. This almost seems to destroy the only theory offered, and rather to suggest simply the influence of chance in the growth of transplants. Lastly, to the question whether it is easier to bring about by experimental means the transformation of a benign into a malignant tumor than to effect a similar transformation of normal tissue, little can be given. The author suggests that growth energy in benign tumors should be studied with the aim of producing an increase in this quality. Up to the present, the decreased growth energy demonstrated in the transplantation of these tumors gives little encouragement to the prospect of inducing malignant change in benign tumors.

The Inheritability of Spontaneous Tumors of Specific Organs and of Specific Types in Mice.—During the past few years, much valuable work has been completed on experimental tumor growth. Mice have been most widely used in this type of study. As a result, certain definite postulates have been established, notably by Slye, who has maintained a large colony of mice of various strains under ideal hygienic conditions for a period extending over ten years. This has facilitated a careful study of the heredity of the animals used and has also produced a rugged stock, capable of living well over the tumor-bearing age. Following these strains, it has been possible to show that tumor development has a persistent tendency to recur in strains where it has been introduced by breeding. This persistence withstands both inbreeding and hybridization. Other strains, non-cancerous, have never developed tumor, either by inbreeding or by hybridization with proved noncancerous strains. Cancer can be introduced into non-cancerous strains, however, by hybridization with cancerous individuals, and from such crosses it is possible to obtain strains which never produce cancer as well as strains which always do, and which carry it into any strain with which they may be hybridized. Hence, the behavior of mouse cancer in heredity is similar to that of a Mendelian recessive characteristic. SLYE (*Jour. Cancer Res.*, 1916, i, 479) now reports some concrete instances of heredity. In a strain of Japanese white-footed mice, which has presented many tumors of all types in addition to the commoner ones of breast and lung, there gradually developed a period of remission in which tumors became rarer, and there were very few of the unusual varieties. As the hybrids of this race began to attain the cancer age, the incidence of tumors of all sorts again became high. As an example primary ovarian tumors may be mentioned. Out of the first 2200 autopsies, there were eight primary ovarian tumors; in the next 4000 no ovarian tumors; and in the last 3000 six primary ovarian tumors. The same is true of liver tumors, where more than half of the whole number obtained has been found in hybrids of the original tumor-bearing strain, only now coming to the tumor-bearing age. The author emphasizes in her report that the inheritability of these tumors is strongly brought out by the fact that while this strain has been subject to exactly the same environment as the others of her stock, nearly all the unusual forms of tumor have come from this one strain. Uterine

tumors, also found in this strain, were a further interesting and striking instance of inheritance of a tumor of specific type in a specific organ. A female, inbred with her brother, gave rise to a strain producing 3 out of the 4 uterine tumors found in the entire group of animals studied in the first 2000 autopsies. Outbred with a male of another group, she obtained a strain producing the only other uterine tumor of the same series of autopsies, and in addition, her direct descendants by both inbreeding and hybridization, headed families producing further uterine tumors. A suggestion substantiating trauma as an etiological factor is given in connection with a curious fibromatous growth, infiltrative in character, which appears on the back and sides, following repeated light scratches, severe enough to result in scarring. An area of baldness develops, followed by an induration which becomes deeper rather than wider. Finally the entire posterior portion of the body undergoes a stiffening, and death results from inability to move to food and water. This form of tumor is inheritable, and has been followed through two successive generations. The author thus claims that tumors of specific organs and specific types are inheritable, and that by selective breeding it is possible to develop a higher percentage of any type of tumor, which may then be carried into another line, free of tumor, and run true to form in the offspring. In another paper (*Jour. Cancer Res.*, 1916, i, 503) the author develops this theme further, in a study of the inheritability of spontaneous tumors of the liver in mice. This type was selected as one which would offer substantial evidence on the influence of inheritance on tumor development as this tumor is not so frequently found as those in the lung and breast, nor is it so rare as to be questioned, as might be the case with tumors of the uterus and stomach. All the liver tumors, including 62 primary and 17 secondary liver tumors, have come from one strain and the animals showing this type of new growth all have an identical ancestry. A few examples will serve to illustrate the manner in which the details have been worked out. A male having an adenoma of the liver, mated to a female with liver tumor, gave a family in which there was a high percentage of liver tumors. The same animal, mated to a female without liver tumor showed no liver tumor in the offspring, though the percentage of tumor in this family was high. Another strain, especially selected to show the inheritability of liver tumor, was sired by a male with a malignant adenoma of the liver. The male offspring constantly showed tumor, though always bred to a female without tumor, and not of the direct line. In the fifth and sixth generation, primary liver tumors again appeared. The data presented appear convincing, especially since outside of the author's stock, but one instance of liver tumor has been reported and in view of the fact that in attaining these results selective breeding has been the only manipulation employed.

On the Etiology of Scarlet Fever.—The infecting agent of scarlet fever still baffles the investigator. Periodically researches are undertaken in an attempt to determine the infecting microörganism and often some bacterium is found, which, though satisfying the investigator in his studies, has proved disappointing to others in failing to fulfil the requirements proving it the causative factor of scarlet fever. During 1916 two new microörganisms were offered by independent

workers as the etiological factor of scarlet fever. MAIR (*Jour. Path. and Bact.*, 1916, xx, 366) isolated from the throats of scarlet fever patients a micrococcus which he called the Diplococcus scarlatinæ and which on cultivation showed itself to be related either to the pneumococcus group or to the group of streptococcus viridans. Mair himself believed that the relation with the pneumococcus was quite close, although capsules as a rule could not be demonstrated. The microorganism produced green colonies on blood agar, caused milk to clot and become acid, and fermented many of the carbohydrates including lactose, salicin and inulin. Mannite was fermented by some strains but not by all. The microörganism dissolved in bile, a characteristic which is distinctive of the pneumococcus. A low pathogenicity was demonstrated for mice and rats while rabbits showed a greater susceptibility. Guinea-pigs were fairly refractile. The author claimed to have obtained peculiar reactions in the monkey associated with fever, Doehle's bodies in the leukocytes and a spreading inflammation beneath the skin. Local sloughing or abscess formation ending in recovery or toxemic death in the second, third or fourth week in treated monkeys, was regarded as typical by the author for the Diplococcus scarlatinæ. Control experiments, using typical pneumococci from other sources, gave no such reactions. A certain grade of immunity was conferred upon infected monkeys which recovered. The author was able to isolate the microörganism from the throat of 42 patients out of a total of 50; while, in a control series of 35 cases, no organisms corresponding to the Diplococcus scarlatinæ were found, although from 12 of them typical pneumococci were obtained. In concluding upon the specific nature of the Doplococcus scarlatinæ, the author placed weight upon the finding of this microörganism in 80 per cent. of the cases, the reproduction in the monkey of "a disease which in many respects resembles scarlet fever," and the development in the monkey of "scarlatinal rheumatism." The rash of scarlet fever has not been observed in animals. Almost simultaneously with the report by Mair, a preliminary note upon the same subject was issued by MALLORY and MEDLAR (*Jour. Med. Res.*, 1916, xxxiv, 127) and was subsequently followed by a more extensive paper (*Jour. Med. Res.*, 1916, xxxv, 209). These studies were mainly of a histological kind, wherein tissues obtained at autopsy from cases of scarlet fever were analyzed. These studies were supplemented by cultural methods upon about 60 patients. The authors found a Gram-positive bacillus (B. scarlatinæ) which is usually less virulent than the diphtheria bacillus but which, as a rule, affects the the same localities, the tonsils and pharynx, and in severe cases may extend to the adjoining tissues. The organism is held responsible for the necrosis of the lining epithelium and the exudation of serum and leucocytes occurring in the deeper structures. In uncomplicated scarlet fever the bacilli were found in large numbers in lesions in the respiratory tract, from which, however, they rapidly disappeared following the appearance of the eruption. Occasionally the microörganisms were found for longer periods of time. On three occasions a similar bacillus was found in stained sections of postmortem material, while cultures of a similar microörganism were obtained in five instances at autopsy. The bacillus was smaller than that of diphtheria but appeared to belong to the same group of microörganisms. In a few instances

serum from scarlet fever patients gave a positive complement-fixation test. Animal experiments using monkeys, rabbits, guinea-pigs, rats and mice gave inclusive results.

War Nephritis.—The present war has demonstrated many new phases in the development of disease as well as brought to light a number of conditions previously unknown to medical literature. The very character of the warfare on land has placed the individuals of the armies under conditions which have heretofore been entirely unknown to civil and military life. The trenches, although not new, have been developed upon such a scale that the soldier makes his home day and night in these constructions, which at different seasons in the year place him under conditions, particularly in exposure to wet and cold, to which he has been unaccustomed. Furthermore, the enormity of the armies gathered upon the field of war is so tremendous that the hygienic handling is one of great difficulty. There are, therefore, many circumstances which may influence the spread of infection and the development of disease. RUDOLPH (*Canadian Med. Assn. Jour.*, 1917, vii, 289) in a recent communication discusses the occurrence of war nephritis or what others have presumed to call "trench nephritis." This disease is not entirely new, as it was observed in the Civil War. The author had an opportunity of seeing about 200 cases of this condition. Its development in the army occurs almost in epidemic form so that in certain seasons numerous men seek the hospital for renal disturbances. Rudolph points out that the term trench nephritis is a misnomer for it is unnecessary to have lived in the trenches to suffer the affection. In the majority of instances the individuals had previously been robust and without an ailment. A few had had an antecedent sore throat or bronchitis. Edema was an early manifestation and was commonly the condition which warned the individual of his trouble. Headache was not uncommon and nocturnal dyspnea occurred in 78 per cent. A rise in blood-pressure was noted in about one-half of the cases studied. In a number of instances the nephritis was a recurrent one, the individual giving a history of previous illness having no relation to the military conditions. The cases which were clearly primary varied from mild to very acute attacks showing coma and convulsions. In the series reported 6 per cent. had convulsions. Only one case died and this was a recurrent one with small granular kidneys. The author believes that the condition has its basis in infection and is of the nature of a glomerulonephritis.

The Pathological Effects of Streptococcus from Cases of Poliomyelitis and Other Sources.—BULL (*Jour. Exper. Med.*, 1917, xxv, 557) inoculated guinea-pigs, cats, dogs, rabbits and monkeys with cultures from the tonsils of 32 cases of poliomyelitis; carrying on, in other words, the same experiments as Mathers, Herzog, Nuzum and Rosenow. His results were widely different from those of these previous authors who claim to have produced poliomyelitis clinically and pathologically by the inoculation of streptococci into the same laboratory animals. In no case was the author able to induce conditions resembling poliomyelitis either clinically or pathologically. A considerable percentage of rabbits and a similar percentage of some of the other animals developed lesions

due to streptococcus, such as meningitis, arthritis, endocarditis, abscesses of kidney or brain, etc. Seventy-eight rabbits received intravenous injections of cultures from poliomyelitis patients; 76, cultures from non-poliomyelitic sources. The distribution, character and frequency of the lesions were the same in both series. Moreover, conditions and lesions were produced in rabbits not found in man or the monkey. The author was also unable to detect any immunological relationship between the streptococcus and the filterable virus of poliomyelitis. Monkeys immunized against streptococci developed poliomyelitis when inoculated with the filterable virus. Streptococci isolated from the poliomyelitic brain and spinal cord of monkeys which had succumbed to inoculation with filtered virus failed to induce in other monkeys any paralysis or change characteristic of poliomyelitis.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Cultivation Experiments with the Blood and Spinal Fluid of Pellagrins.—FRANCIS (*Hyg. Lab. Bull.*, No. 106) carried out anaërobic cultivation on the blood and spinal fluid of pellagrins, somewhat after the method described by Noguchi for growing spirochetes. Blood and spinal fluid were cultured from each of 17 colored pellagrins at the State Insane Asylum, Milledgeville, Georgia, 7 of which proved fatal between six and thirty-seven days after the materials were obtained from them. In addition, blood was cultured from 4 mild cases at the U. S. Marine Hospital, Savannah, Georgia. Each inoculated culture tube contained (*a*) fresh rabbit kidney; (*b*) either ascitic fluid or a mixture of 1 part ascitic fluid and 2 parts meat-infusion agar (+0.5), which latter, in some cases, contained 2 per cent. of glucose; (*c*) either fresh spinal fluid drawn by lumbar puncture or fresh blood drawn from the median basilic vein (defibrinated or citrated); (*d*) either a 1-inch column of sterile paraffin oil or no oil. All culture tubes were incubated without the use of special anaërobic apparatus at 37° C. for two or three weeks, at the end of which time examinations were made with the dark-field microscope. The method of cultivation employed furnished conditions of growth suitable for strict anaërobes, strict aërobes, and for facultative organisms of either group. Anaërobic conditions were most nearly approached around the kidney tissue at the bottom of the oil-covered tubes. To a less degree there

was anaërobiosis at the bottom of the uncovered tubes. Conditions for aërobic growth were found on the surface of those tubes of the media which were not covered with oil. There were thus studied eight culture tubes inoculated with 10 c.c. of blood drawn from each of 21 cases and eight culture tubes inoculated with 10 to 20 c.c. of spinal fluid drawn from each of 16 cases, making a total of 296 tubes examined. The results of the examination of the cultures were negative; the cultures either remained sterile, or an occasional tube showed a growth which was evidently a contamination.

The Transmissibility of Pellagra. — GOLDBERGER (*Public Health Reports*, November 17, 1916, xxxi, No. 46) subjected sixteen volunteers to experiment. With one exception all were men and varied in age from twenty-six to forty-two years. No restraints were imposed on their customary habits or activities. Seventeen cases of pellagra of various types and of different grades of severity furnished some one or more of the experimental materials. The materials were blood, nasopharyngeal secretions, epidermal scales from pellagrous lesions, urine and feces. Blood was furnished by 4 of the cases, nasopharyngeal secretions by 4, epidermal scales by 5, and urine or feces by 16, of whom 10 furnished both urine and feces, 3 urine without feces, and 3 feces without urine. Blood was administered by intramuscular or subcutaneous injection; secretions by application to the mucosa of the nose and nasopharynx; scales and excreta by mouth. Both urine and feces were ingested by 15 of the volunteers, 5 of whom also took blood, secretions, and scale. The experiments were performed at four widely separated localities (Washington, D. C.; Columbia, S. C.; Spartanburg, S. C.; and New Orleans, La.) at which different groups of the volunteers were assembled. Observation has been maintained by association with a majority of the volunteers and by visits of inspection, supplemented by reports from the volunteers themselves, 13 of whom are physicians, and by reports from other medical officers of the service with whom they are associated. During a period of between five and seven months none has developed evidence justifying a diagnosis of pellagra. These experiments furnish no support for the view that pellagra is a communicable disease; they materially strengthen the conclusion that it is a disease essentially of dietary origin, brought about by a faulty, probably "deficient" diet.

The Effect of Cold upon Malaria Parasites in the Mosquito Host.— KING (*Jour. Exper. Med.*, March 1, 1917, xxv, No. 3) reports experiments showing that the parasite of tertian malaria in the mosquito host is able to survive exposure to a temperature of 30° F. for a period of two days, 31° F. for four days, and a mean temperature of 46° F. for seventeen days. In a smaller series of tests the sporonts of the estivo-autumnal parasite have shown a resistance to temperature as low as 35° F. for twenty-four hours.

The Application of the Statistical Method to Public Health Research. —DUBLIN (*Am. Jour. Public Health*, vii, No. 1) discusses the commoner fallacies and errors that arise in statistical investigations in the field of public health and hygiene. He divides statistical investigations into three stages: (1) Defining the scope of the inquiry, planning

the inquiry schedule, and collecting the data; (2) editing, classifying and tabulating the data; and (3) analyzing and interpreting the results. He points out with many illustrations the fallacies and errors that arise at each stage. In the first stage of public health investigations, the author thinks, errors often result from poorly devised questionnaires and from the incomplete registration of facts. In the second stage, he emphasizes the importance of properly editing the schedules before tabulation and of returning defective schedules to the original source of correction. The use of standard systems of classification is emphasized and errors that result from indifference to the use of standard systems are considered. The gravest errors in the use of the statistical method in public health work, the writer says, arise in the third stage of inquiry, i. e., in the interpretation and analysis of the results. The investigator should make every effort to avoid errors of this kind because it is in this part of the inquiry that the public is most interested. Among the commoner fallacies of analysis are those which arise from the comparisons of statistics that are essentially incomparable, from a confused idea that "proportions" are somehow equivalent to "rates," from the drawing of conclusions from too few cases and the like. In conclusion, he points out the necessity for extreme caution in the collection, preparation, and interpretation of data in public health work. This is necessary if the general public is to be expected to support health movements based on the results of such investigations. Health officers will find in this paper many practical suggestions, that will help them in the research side of their work.

Pertussis Vaccine.—PAUL LUTTINGER (*Jour. Am. Med. Assn.*, May 19, 1917, lxviii, No. 20, 1461) gives a summary of the results of the whooping-cough clinic of the Department of Health of the City of New York. The work was carried out under the supervision of Dr. William H. Park, and the conclusions reached are that the results obtained at the clinic, and also by over 180 private physicians and health officers would warrant the routine administration of pertussis vaccine for both curative and prophylactic purposes. The best time to institute the vaccine treatment, except as a prophylactic, is the first and second week of the paroxysmal stage. When the proper vaccine is given and the method of the department is employed, the disease is materially reduced in duration and severity. The presence of subconjunctival hemorrhages in prophylactic cases which were protected by the vaccine seems to point to its specific immunizing action against the paroxysms and to the fallacy of the hitherto accepted theory that these hemorrhages are due to the violence of the cough.

The Possibility of Typhoid Infection through Vegetables.—MELICK (*Jour. Infect. Dis.*, July 1, 1917, p. 28) reports that the longevity of B. typhosus in soils has shown considerable variations under like conditions in the open. The old strains (1 and 3) survived in garden soils fifty and fifty-three days, while the viability of fresh cultures (strains 4 and 5) was thirty-two and forty-three days, respectively. In sandy soil the longevity of strain 3 was thirty-six days; that of strain 4, twenty-nine days. In three outdoor experiments, extending from May to September, B. typhosus was isolated from garden soil inoculated

with typhoid excreta after forty-one, thirty-four and thirty-five days. Under hot-house conditions in sandy soil, strain 1 survived fifty-three days. The longevity was increased under the same conditions in garden soil enriched with sterile sewage and broth to seventy-four days. Similarly, the viability of fresh culture of strain 2 in garden soil was forty-nine days. No evidence has been found that would indicate the entrance of B. typhosus into the interior of the plants. The organisms become attached to the surfaces from their contact with the soil and are not removed by ordinary washing. Under natural conditions, radishes grown in contaminated soil were found to be still infected with typhoid bacilli in 3 experiments after periods of thirty-seven, twenty-eight and thirty-five days, respectively; and from lettuce, after twenty-one days. This is ample time for the maturing of such vegetables. It may be reasonably concluded that vegetables grown in soil fertilized with fresh typhoid excreta shortly before planting or during the growing season are likely to be contaminated at the time they reach the consumer. Vegetables so contaminated are not made safe by the ordinary method used in the preparation of such foods for table use, and may, therefore, be a source of typhoid infection.

The Focal Pulmonary Tuberculosis of Children and Adults.— Opie (*Jour. Exper. Med.*, June, 1917) examined fifty adults and found evidence of tuberculosis infection in all of them. Approximately one-half of all adults have encapsulated lesions of the lungs or bronchial lymphatic nodes, whereas in one-third pulmonary and lymphatic lesions are firmly calcified and completely healed. Tuberculosis pulmonary lesions of adults who have died of diseases other than tuberculosis are of two types: (1) apicaltuberculosis similar to the usual type of fatal phthisis and unaccompanied by caseation of the regional lymphatic nodes; (2) focal tuberculosis not more commonly situated in the apices of the lungs than elsewhere and accompanied by caseation (or calcification) of the adjacent lymphatic nodes. Focal pulmonary tuberculosis of adults is identical with the tuberculosis of childhood. It occurs in at least 92 per cent. of all adults. It may be acquired between the ages of two and ten years but in more than half of all individuals (in St. Louis) makes its appearance between the ages of ten and eighteen years. Tuberculosis of children does not select the apices of the lungs, is accompanied by massive tuberculosis of regional lymphatic nodes, and exhibits the characters of tuberculosis in a freshly infected animal, whereas tuberculosis which occurs in the pulmonary apices of adults has the characters of a second infection. Almost all human beings are spontaneously "vaccinated" with tuberculosis before they reach adult life.

Methods for the Determination of Pneumococcus Types.—Blake (*Jour. Exp. Med.*, July 1, 1917, p. 67) states that the determination of pneumococcus types in lobar pneumonia is of value in the field of prognosis and as a prerequisite for specific serum therapy. The method for the determination of types should be as rapid as possible and a standard technic should be employed. The most satisfactory method is by the intraperitoneal inoculation of a mouse with the patient's sputum, by which means a rapid and abundant growth of the pneumococcus is

obtained and secondary organisms are rapidly eliminated in most instances. The diagnosis of type is made directly on the peritoneal exudate. Certain factors in the method commonly used have interfered with the rapid determination of types in an appreciable number of cases, notably the growth of other organisms in the peritoneal exudate together with the pneumococcus, and some confusion has arisen because occasional strains of pneumococci have been encountered that show cross agglutination reactions when undiluted immune serum is used. Such reactions have been shown to be due to a limited zone of non-specific immunity and they in no way invalidate the classification of the pneumococci into sharply defined immunological groups. The optimum dilutions of serum have been determined that will agglutinate all type trains of pneumococci and fail to cause any cross-agglutination reactions when mixed with equal amounts of pneumococcus cultures and incubated for one hour at 37° C. They are a 1 to 20 dilution of serum I, a 1 to 20 dilution of serum II, and a 1 to 5 dilution of serum III. For the diagnosis of subgroup II pneumococci undiluted type II serum is required. To obviate the other difficulties of the method commonly used a new method for the determination of types has been devised. It depends upon the fact that there is produced by the growth of the pneumococcus a soluble substance which is present in the peritoneal exudate of the mouse in sufficient quantity to give a specific precipitin reaction with the homologous immune serum. The precipitin method can be used in all instances in which the determination of types by the agglutination method is possible, and it possesses certain distinct advantages which make it available when the agglutination method is impracticable. It is of particular value as a time-saving device in those instances where the presence of other organisms together with the pneumococcus in the peritoneal exudate causes a delay of eighteen hours or more before the type of pneumococcus can be definitely established. It is therefore recommended as the method of choice in all cases. If desired, both the agglutination and precipitin methods may be applied to the same specimen of peritoneal washings.

Rocky Mountain Spotted Fever in California.—KELLY (*Public Health Reports*, vol. xxxi, No. 40) as a result of an investigation of Rocky Mountain spotted fever in Modoc and Lassen Counties, California, reaches the following conclusions: (1) Rocky Mountain spotted fever has existed in California for a much longer period and to a far greater extent than has hitherto been supposed. (2) There are probably five main infected areas, one in Modoc County and four in Lassen. (3) The disease is not as severe in California as in Montana, nor as light as in Idaho. (4) The infection probably entered California through Nevada rather than Oregon.

ORIGINAL ARTICLES

THE UTILIZATION OF THE IMMUNE RESPONSE IN RENAL TUBERCULOSIS.[1]

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The usual path of the patient suffering from renal tuberculosis leads first to the family doctor or general practitioner who treats such patient for every conceivable urethral, prostatic, and bladder condition, and occasionally kidney condition, except tuberculosis. After a varied sojourn under the treatment, the patient finally gets to the genito-urinary surgeon or gynecologist, who finds the condition advanced and resorts to nephrectomy. And so it happens that the path of the patient steers him clear of the immunotherapeutist. Thus our literature, as to the value of the utilization of the immune response in renal tuberculosis, is still too meager to draw conclusions. My task therefore is not an easy one, for not only must I meet the great and general prejudice that exists against the use of tuberculin, but I must join the spare ranks of the advocates of tuberculin in the renal form of this protein infection.

As far as precedents are concerned, let us rather remember the utter misery that is the lot of the patient suffering from renal tuberculosis even after extensive operations than refuse a therapeutic agent that might prove beneficial because of lack of proof as to its value in the past. That, as a general rule, renal tuberculosis is diagnosed after considerable extension of the process; that per-

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[1] Read before the New York Physicians' Association, January 25, 1917.

manent damage results from such process no matter how proficient the therapeutics may be if instituted late; and finally, that an early diagnosis is essential in the production of a permanent cure, are facts that can be accepted as axiomatic. This being the case, it can easily be seen that our most important task in renal tuberculosis is an early diagnosis. But before we discuss the subjects of an early diagnosis and early treatment, we shall speak of the treatment of renal tuberculosis as it presents itself to us at the present time.

PRESENT-DAY TREATMENT. It is well known that the treatment of any part of the genito-urinary tract is very complicated and difficult no matter what the cause of the pathological process may be. We all know how prone to chronicity is any condition arising in the kidney or any part of the genito-urinary tract. When a posterior urethritis remains for years it is not because the infection with the gonococcus differs from the infection with any other organism, for when the colon bacillus produces a pathological process in the pelvis of the kidney it is often equally tenacious. Even the non-infectious inflammatory processes attacking the kidney leave behind permanent damage. It is the complexity of the mechanism of the urinary apparatus, and the replacement of destroyed parenchyma by non-functioning connective tissue, especially of the kidney, that render any pathological process liable to make the result of its ravages permanent. The longer the pathological process progresses the greater the resulting destruction after the cure of the infection. To overlook this fact means to do a great deal of injustice to immunotherapy. It has been the tendency in the profession to apply this form of therapy as a measure of last resort after a great deal of destruction has already occurred, and when the symptoms referable to the permanent damage resulting from the destruction have necessarily to remain even after the total eradication of the etiological factor. Unfortunately, these symptoms are immediately attributed to the failure of immunotherapy. And since most cases that have been treated in the past with tuberculin are hopeless cases to begin with—that is, postoperative cases, with extension into the remaining kidney, or bilateral renal tuberculosis, in which symptoms due to the distorted urinary apparatus will remain—the elimination with tuberculin of tuberculosis as an infection has not been realized. On the contrary the persisting symptoms, although due to the distorted apparatus, are propounded as evidence of the failure of tuberculin.

Besides the element of permanent damage that tends to minimize the results of tuberculin treatment we have another important factor which makes for the continuation of the pathological process. The matter of mixed infection, for instance, has been entirely overlooked, by some unintentionally, in failing to realize its importance as a factor in the formation of the whole picture

of urogenital tuberculosis; by others who, in using tuberculin, expected all the symptoms, including those caused by mixed infection, to disappear as the only means of "testing" the efficacy of tuberculin. It has been long evident to those who have had considerable experience with tuberculin that a persistent mixed infection may continue the entire pathological process even after the tubercle bacillus has been entirely eliminated as a factor. Frequently, we have treated cases for a period of months without apparent results, only to discover that the prominent subjective symptoms were due to the mixed infection, and that autogenous vaccine made from the urine and administered would do more, subjectively, in a few treatments than the tuberculin accomplished in months. By this statement I do not wish to be misunderstood to mean that in such instance vaccine should have been used instead of tuberculin to begin with. On the contrary, we must remember that the infection with the tubercle bacilli is the main etiological factor which must be eliminated by all means, for the elimination of the mixed infection alone would give only temporary relief. At the same time the failure to remove the mixed infection by vaccine would mask the good results from tuberculin, and for all practical purposes would count as a failure for tuberculin.

In view of the fact that tuberculosis of the kidney is not a primary infection, but that the source of infection is elsewhere, probably most frequently from the mesenteric glands, what are the chances for recovery following nephrectomy alone? The removal of a kidney is an operation of considerable magnitude and serves to increase the tubercular hypersusceptibility to a high degree. The infection from the remaining kidney from the same source becomes even more likely than the infection of the first kidney, and we know with what frequency the infection of the remaining one occurs. Occasionally, the patient is cured after the removal of the kidney. One source of the infection was in that case completely healed, so that the removal of the kidney was sufficient to stop the rest of the tubercular process, just as the radical operation in glands of the neck does get beyond the area of infection at times. However, the cases in which there is extension of the disease, or at least when there is no benefit to the patient after the removal of the kidney, are of such frequent occurrence that the operation can hardly be called a success.

On the other hand, in the majority of cases in which the principal cause of all the symptoms is a slowly progressive tubercular infection, how can we expect to cure the patient with the extirpation of the kidney? Not only do we leave behind a tubercular process in the urinary tract below the removed kidney, but with the added burden suddenly thrown upon the remaining kidney its . resistance may be momentarily lowered and an infection from the circulation may begin here. The hypersusceptibility, increased as

a result of the operation, will more than encourage this occurrence and bring about a most hopeless condition.

Would it not seem rational to remove the hypersusceptibility by a course of tuberculin treatment and so raise the patient's resistance before nephrectomy is resorted to? The treatment with tuberculin will not only prevent an extension of the process to the other kidney, but will limit the operation to a kidney that is destroyed beyond repair.

Almost as much can be said of the vaccine treatment of mixed infections. A superimposed colon bacillus infection upon a tubercular process may be producing the principal symptoms in an acute condition. The use of vaccine may frequently remove the urgency of an operation. It will nearly always convert the necessity of a serious operation in an acute state to the safer operation during a controlled infection. This is also true in the case of mixed infections due to the streptococcus, staphylococcus, pyocyaneus, pneumococcus, etc.

Let us now turn to the subject of early diagnosis and treatment. We all know that in most cases of renal tuberculosis the early symptoms are practically the same as are found in any of the mildest pathological processes occurring in the urinary apparatus. For this reason, when a patient first applies to the physician for treatment the thing remotest from the physician's mind is tuberculosis, and even were it suspected the usual process of making a diagnosis requires the services of a specialist. Cystoscopy, guinea-pig inoculations, etc., involve not only a considerable expense but a great deal of time and discomfort on the part of the patient, all of which, in view of the mildness of the symptoms, neither the physician nor the patient would deem justifiable. The problem, therefore, resolves itself to the utilization of the tuberculin test, which is simple enough to be applied by the general practitioner to whom the patient first applies; and not only is it devoid of inconvenience and expense to the patient, but is far more reliable than any other means at hand for an early diagnosis.

TUBERCULIN IN DIAGNOSIS. The chief reason for the neglect of tuberculin in diagnosis at the present time is the fact that the mechanism of tuberculin diagnosis has been too little understood by a great many of those who have utilized it in the past. The elements that entered into its misapplication were (1) the failure to realize that a suspicion of a tubercular active lesion is presupposed when a test is made and that a production of a constitutional reaction is prejudicial to the case if an active lesion exists, and (2) that the mere rise in temperature as a result of tuberculin inoculation is in itself of no value in the diagnosis.

The scope of this paper does not permit of a detailed description of tuberculin in diagnosis. I can only include the essential points, and these are that the smallest amount of tuberculin should

be used which will produce a constitutional reaction in each case. That can be determined by producing such a reaction by three or four inoculations forty-eight hours apart, beginning with 0.0001 c.c. of O.T. and increasing each succeeding dose to about five times the last dose until a temperature of 1°, or as little as possible above that, is produced instead of endeavoring to obtain a temperature by one inoculation in all cases. The final dose of 0.001 of O.T. if negative will determine the test. And so we render the test safe. The diagnostic feature of a tuberculin test is not a local reaction at the point of inoculation, nor is it in the rise in temperature— it is the focal manifestations that occur during the constitutional reaction. The focal reaction consists of a hyperemia around the active lesion wherever that may happen to be, with the consequent exaggeration of symptoms that go with the organ in which the lesion occurs. Being in the kidney the focal manifestations will lead to a marked increase in frequency of micturition, any pain or discomfort will be exaggerated, and very frequently tubercle bacilli will appear in the urine during the constitutional reaction when repeated examinations previous to the test failed to demonstrate them.

When shall we resort to the tuberculin test? We know that by far the most common symptoms in renal tuberculosis is frequency of micturition. If every case of frequency would be subjected to the tuberculin test an early diagnosis would be made far more usual than it is at the present time. Aside from frequency, any symptoms referable to the urinary apparatus for which a definite pathological process other than tuberculosis cannot be definitely ascribed should be an indication for the subcutaneous tuberculin test.

One characteristic example of the value of tuberculin in early tuberculosis is the following:

Mr. R., aged fifty-two years, born in the United States.

Family History. Negative.

Past History. Shows a physical condition far above the average. From 1886 to 1887 was on the Columbia Football Team (before the game was modified), weighing 180 pounds and measuring six feet in height.

Present History. On one of many visits with his daughter, whom I am treating for colon bacillus infection, he incidentally remarked that he was troubled, for three or four months, with frequency of micturition. He apologized for mentioning it at all, as he thought the matter trivial; but since recently the frequency occurred also at night he thought better to mention it. He complained of no pain of any kind. A specimen of the urine, freshly passed, showed no trace of abnormality. When I explained that while, on the other hand, it might be a small matter, perhaps an enlarged prostate or improper food or something coming on incidental to his age, but that, on the other hand, it might point

remotely to something more serious and that a thorough investigation would be advisable, he readily submitted. A laboratory analysis of the urine showed no abnormality. A four-day temperature prior to the test was taken and found to be normal. During the same four days a census of the frequency was taken and found to be nine to eleven times in twenty-four hours, with the total quantity of urine passed between 50 and 60 ounces in twenty-four hours. At the end of the four days 0.0001 c.c. of O.T. was administered subcutaneously without any effect. Forty-eight hours later 0.001 c.c. of O.T. was administered late in the afternoon. The following day the patient reported a temperature of 100.5° and a few hours later 101°. Marked local reaction at the point of inoculation and pain and aches throughout the body he tried to attribute to an attack of la grippe. A specimen of urine voided during the height of the temperature was sent to the laboratory. The report showed numerous tubercle bacilli. Following the inoculation the frequency numbered seventeen times. A dragging pain, more pronounced on the right side, led to the inference that the tubercular process was in the right kidney. The marked increased frequency during the constitutional reaction was more diagnostic than the rise in temperature itself. It indicated a focal reaction, which could only take place in an active tubercular lesion, and even without the discovery of tubercle bacilli in the urine would have been absolutely diagnostic. All symptoms disappeared at the end of forty-eight hours, and the frequency promptly diminished to the same degree as it had existed before the reaction. Repeated bacteriological examinations of the urine after the abatement of the constitutional reaction failed to reveal the tubercle bacilli.

With an early diagnosis established, how shall we proceed with our treatment? I do not know of anyone who would advocate the removal of the kidney when an early diagnosis is made. There remains only the hygienic-dietetic and climatic treatment to be instituted for a patient when an early diagnosis is made. And what can that offer us? Unlike the patients with pulmonary tuberculosis, this class of patients are usually in good physical condition, and if a fine physical condition did not prevent the lesion from starting in the kidney, how can we expect a treatment which depends upon the improvement of the physical condition to cure or even check the disease? Here we deal with a combination of circumstances, all of which are already favorable to the production of a natural immune-response against the tubercle bacilli, except that the mechanism producing the immune response is faulty. The stimulation of this mechanism with tuberculin remains the only logical early treatment. All other resources necessary for the patient's own defence are already present. The utilization of the immune response in incipient renal tuberculosis consists of two important elements—tuberculin for the treatment of the condition,

and vaccine as a prophylactic against mixed infection. This class of case offers the simplest conditions for tuberculin treatment. At this time the hypersusceptibility is present to only a mild degree, and severe reactions will rarely occur. With the safer method of tuberculin administration now in use at the New York Polyclinic Hospital there is no difficulty in its utilization in general practice.

As to the results obtained with tuberculin, I can only say, as I have said before, that owing to the failure in making an early diagnosis the treatment of the early condition was impossible in the past. But in the presence of such reports as come from Karo and Mantoux and from Hohlweg and others who report such striking results from the utilization of tuberculin in renal tuberculosis, and that in cases in which a diagnosis was certain through the usual methods—in other words, in advanced cases only—can we not expect that in early cases the results would be even better? In our experience we have but a few cases to help us, all of which have been cases of long-standing bilateral tuberculosis or cases of extension of the tubercular process after nephrectomy. In view of distinct beneficial effects of tuberculin in these conditions, how can we doubt its efficacy in incipient tuberculosis of the kidney? On the contrary, the treatment of early renal tuberculosis with tuberculin is not unlike the treatment of tubercular cervical adenitis, in which condition its efficacy is no longer doubted. As regards the utilization of tuberculin in the early diagnosis of renal tuberculosis I have begun its use here but recently, and so I am not ready to report on the treatment of these cases with tuberculin. But I hope, in view of present indications, to have a report to make in the near future which will not fall short of our expectations.

The second element in the treatment is almost as important, and that is the prophylactic immunization against imminent mixed infection. Bacteria are constantly carried through the kidneys. Especially is this true of the colon bacillus. Mixed infection with the colon bacillus and the streptococcus and the staphylococcus form the constant menace to the favorable progress of the infection during the treatment of renal tuberculosis. In fact, the longer I observe these cases the more I am convinced that a mixed infection is responsible in the vast majority of cases for the spread of localized tubercular lesion in the kidney. Three inoculations with a stock vaccine of the colon, and Streptococcus and Staphylococcus albus should be given a week or ten days apart. The first two inoculations consists of 250 mil. each of the colon and the streptococcus and 1000 mil. of the Staphylococcus albus, and the third inoculation consists of 500 mil. each of the colon and the streptococcus and 2000 mil. of the staphylococcus. There is a much greater field in the prophylactic immunization against imminent localized infection than we are aware of at present, and I hope in the near future to be able to report upon it more fully.

SUMMARY. To recapitulate (1) the prognosis in renal tuberculosis up to the present has been unfavorable under the present-day method of treatment. Nephrectomy as an operation for the relief of the patient suffering from tuberculosis in the kidney is a failure, for it fails to remove the focus of infection outside of the kidney, leaving the patient liable to extension of the infection to the remaining kidney from the same focus. The tuberculin treatment of renal tuberculosis has not been as satisfactory as the tuberculin treatment of other forms of tuberculosis, because of the inability to make an early diagnosis; (2) because of the production of early damage before the tuberculin treatment was instituted; (3) as a result of the failure to recognize the important role that mixed infection plays in the production of symptoms and pathological processes. However, enough has been shown with tuberculin treatment of renal tuberculosis, in fact, to make it almost certain that were it instituted before permanent damage has resulted—in other words, early in the disease—the prognosis of renal tuberculosis would have a far more favorable aspect. Early diagnosis in renal tuberculosis can be accomplished through the tuberculin test alone. Its more frequent use in early symptoms referable to an indefinite lesion anywhere in the urinary tract is absolutely essential to the more hopeful treatment of renal tuberculosis.

THE PULSE-PRESSURE TEST IN PREOPERATIVE ESTIMATION OF THE RESERVE STRENGTH OF THE CARDIO-VASCULAR SYSTEM.

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ALTHOUGH an enormous amount of work has been done with reference to the cardiovascular system and considerable progress has been made toward clearing up the problems associated with it, we are still without a test, simple and reliable enough for clinical use, for estimating the reserve strength of the heart, or rather the cardiovascular system. In many of the cases of so-called cardiac failure the trouble lies not with the heart itself but with the cardiovascular system and its controlling agents, and it is therefore necessary to consider the system as a whole in estimating its functional capacity. It is the efficiency of the whole system and its ability to compensate for the variable changes incident to the stress and strain to which it is subject that maintain the circulation sufficient for the needs of the organism. For the purpose of specific therapy it is necessary to determine which integral part of the system is at fault, but for estimating how much

strain the cardiovascular system will stand such differentiation is not essential.

It has probably been the experience of every surgeon to lose patients after operation from circulatory failure when this was least expected. The heart seems to be normal in the routine examination with the patient in bed, and the patient, from general appearances, seems to be a good surgical risk, and yet death follows from circulatory failure in from one to three weeks following operation. The following cases, in the service of Dr. Huggins, are examples of the types which stimulated our interest in this field, and a brief synopsis of the histories are given.

Case I.—Mrs. T. M., aged thirty-eight years. No. 514. Admitted October 3, 1911. Diagnosis: Chronic appendicitis; myoma uteri; adhesions of ovaries.

Clinical Condition. Indigestion and pain in right side.

Family History. Negative.

Past History. Always enjoyed good health in childhood. Typhoid fever at thirteen. For last one and a half years has had frequent attacks of palpitation of heart. These come on sometimes without exertion. No shortness of breath on exertion.

Menstrual history negative except severe crampy pains at beginning of periods.

Married thirteen years. One child seven years old. Two miscarriages.

Present Illness. Dates from March, 1907. Patient had a severe pain in region of chest. Had difficulty in breathing. Physician was called and diagnosed trouble as pneumonia at first and later as "gall-bladder disease." Patient was not jaundiced following this, and there was no vomiting. Since then patient has been troubled with indigestion, and there is tenderness in upper right quadrant of abdomen.

Physical Examination. Heart: Sounds are clear. No murmurs. Heart not enlarged. Occasional "extrasystole" is heard on auscultation. Urine negative.

October 5, 1911. Operation by Dr. Huggins. Ether. Right rectus incision. Gall-bladder normal. A long thick-walled appendix bound down by adhesions in mid-portion was removed. Light adhesions about both ovaries were broken up. Uterus contained a fibroid the size of a normal uterus. This was not removed.

Patient made an uneventful recovery. Wound healed well and patient was allowed up on chair on fourteenth day after operation. The following note was made that night by the intern:

Patient seen about 10 p.m., having just been helped from couch to bed. Patient was lying on right side, with arms and legs partly flexed. Eyes partly open; staring, glassy expression; mouth open; respirations labored. Did not reply to questions. Pulse could not be felt at wrist. Carotid pulsation rapid, feeble, and

irregular. About two minutes after first seen patient shuddered and became conscious, and asked if she had fainted. Pulse could then be felt at the wrist, but was very weak and collapsible, varying greatly in force during short intervals. Patient complained of being very tired. Had no pain. Breathing at this time was slightly labored. Patient's face was of deathly gray color and covered with cold perspiration. Cardiac stimulants were given and there was some slowing of pulse and improvement in quality after intravenous injection of strophanthin, but condition remained precarious for twenty-four hours, when patient died.

It is interesting to note that the history, as far as was elicited by the intern, gave no symptoms referable to the cardiovascular system aside from palpitation of the heart, which the family physician attributed to her "gall-bladder disease." Physical examination of the heart showed nothing abnormal except an occasional "extrasystole." At that time we had no electrocardiograph and polygraphic tracings were not taken. The history and physical examination and appearance of the patient were not such as to make one suspect any serious cardiovascular trouble, and yet we feel sure that more careful study in this case would have revealed a narrow margin of safety.

CASE II.—Mrs. J. W., aged forty-six years. No. 1312. Admitted October 13, 1914. Diagnosis: Chronic cervicitis; laceration of perineum; cystocele; rectocele; prolapsus uteri.

Clinical Condition. Falling of womb.

Family History. Negative.

Past History. Usual childhood diseases. Typhoid fever at twelve. Troubled with cough and expectoration in the spring. Has had varicose veins for thirteen years. Has been troubled recently with a "nervous fluttering" in the head and stomach. Constipated for years and has hemorrhoids. Difficulty in emptying bladder. Menstrual history negative. Has had six children and one miscarriage. Puerperia normal. Last child eleven years ago. Instrumental delivery.

Present Illness. First noticed prolapse of uterus after last delivery eleven years ago. This has been worse in the last year. Had a flooding spell at menstrual period eight months ago. Has had two such spells since then, the last one four weeks ago.

Physical Examination. Patient is a large, stout, red-faced woman. Weight 215 pounds. Heart: Point of maximum impulse not seen or felt. Upper border of cardiac dulness begins at second interspace. Right border begins at midsternal line. Sounds at apex and base are clear. No murmurs made out. Pulse regular. Systolic blood-pressure, 110.

Vaginal Examination. Laceration of perineum with wide separation of transversus perineii and levator ani muscles and fascia. Rectocele and cystocele present. Stellate laceration of

cervix with enlargement and presence of considerable scar tissue and cystic degeneration. Profuse mucopurulent discharge. Cervix appears at vaginal orifice when patient strains. Body of uterus is somewhat larger and firmer in consistency than normal, and is retroverted. Adnexa normal.

October 16, 1914. Operation by Dr. Huggins. Spinal anesthesia. Vaginal hysterectomy. Perineorrhaphy. Drainage.

November 2, 1914. Aside from the postoperative pain, gas distention, and difficulty in voiding, patient apparently made a good recovery until the last few days, when it was noticed that patient was short of breath on talking and there was slight cyanosis of lips. Last night nurse heard patient turn over in bed and moan, and on examining her found the patient gasping, and death occurred a few minutes later.

In this case the apparently sudden demise might ordinarily be attributed to embolism, but we have the clear-cut history of very evident shortness of breath on talking, associated with slight cyanosis, for several days preceding death. The size of this patient made the ordinary methods of chest examination almost useless and emphasizes the need of additional measures.

The ability to estimate vital resistance is one of the most important factors in reducing mortality in modern elective surgery. This can probably never be done by instruments of precision, and will always be a matter of personal experience, observation, and judgment; but any test or method which aids those with less ability or confirms the judgment of those most skilled in this field is of great value in surgical work. In practically every operative procedure we subject the circulatory apparatus of the patient to a strain which varies with the extent of the operative procedure and the preoperative and postoperative management of the case. In patients with seriously handicapped circulatory apparatus the success or failure of the treatment depends on the surgeon's ability to judge the reserve strength of his patient and his ability to reduce to a minimum the strain of the whole procedure so as to conserve this strength. To draw on the reserve strength of the patient to such an extent that there is exhaustion to the stage when there is no comeback is fatal to the patient and a serious error of judgment on the part of the surgeon. To draw on the reserve supply more than is necessary is done at the expense of the patient's period of convalescence even though the patient recover.

Since circulatory failure still contributes to postoperative morbidity and mortality, how can we estimate the reserve strength of the cardiovascular system? The character of the pulse, the rate, the regularity or irregularity of rhythm and volume, the sphygmogram, the size of the heart, and the character of its sounds are aids to the surgeon who is weighing the preoperative, operative, and postoperative strain against the reserve strength of the circu-

latory apparatus. There is much of promise in the use of the electrocardiograph in this field, but comparatively few have access to its advantages. In examination of the circulatory apparatus, the tendency is too often to focus the attention on the physical examination of the heart. If the heart sounds are clear and there are no irregularities in rhythm, and the heart is not enlarged, we are prone to pass the circulatory system as normal. Our examination is too frequently anatomical and not functional. Incompetent valves, hypertrophied hearts, and irregular rhythms are only warning signals of possible cardiac insufficiencies. The most deceptive types of cases are those without these gross demonstrable lesions, cases in which there seems to be an exhaustion and loss of tone in the circulatory apparatus, with a small reserve strength. Huggins[1] calls attention to general loss of tissue tone in the whole organism, as is frequently seen in cases with prolapse of the uterus, as a warning signal of poor resistance on the part of the patient, and it is particularly in this class of cases that we find functional inefficiencies of the circulatory system without demonstrable gross anatomical lesions. The musculature of the cardiovascular system seems to share the weakness and lack of tone of the general musculature of the body.

Normally when an individual is subjected to work there is a compensatory response on the part of the cardiovascular system, as is shown by blood-pressure readings. Lowsley[2] found that in a normal individual after exercise there is a rise of blood-pressure as well as pulse-rate. There is a rise of both systolic and diastolic pressures, but there is less rise in diastolic than systolic, so that there is also an increase in pulse-pressure. He obtained the following results after exercise on a stationary bicycle:

Average rise in systolic   pressure in 16 cases   .   .   .   .   32.7 mm.
     "   "   diastolic   "   17   "   .   .   .   .   22.9 mm.
     "   "   pulse   "   17   "   .   .   .   .   18.3 mm.
     "   "   pulse rate   9   "   .   .   .   .   51 per min.

He also found that as fatigue advances the systolic pressure falls.

Middleton[3] found an average systolic rise of 24 mm. and diastolic rise of 12 mm. of mercury after fifty running steps in normal individuals.

Barringer[4] found that normally there is a rise in systolic pressure following exercise, but as exhaustion comes on there is a delayed rise of pressure. He found this delayed rise also present in cases of cardiac insufficiency. In some of his cases of cardiac insufficiency he observed that the blood-pressure reactions to work became

[1] Tr. Am. Gyn. Soc., 1916.
[2] Am. Jour. Phys., 1911, xxvii, 446.
[3] Am. Jour. Med. Sc., September, 1915, p. 426.
[4] Arch. Int. Med., March 15, 1916, p. 363.

less and less marked as work progressed until a stage was reached in which the systolic pressure immediately after work was lower than before the work was begun.

Barringer and Teschner,[5] in a previous article, state that sometimes the systolic pressure after work was found to be lower than beforehand, and that this is to be considered as an extreme type of delayed reaction, and means that the heart has been decidedly overtaxed by the preceding work. Graupner[6] states that if blood-pressure after work is lower than normal and then slowly returns to normal, but does not rise above normal, a primary myocardial weakness exists and this reaction is characteristic of pathological insufficiency. The significance therefore of a fall in systolic pressure immediately after work has been recognized and emphasized.

Warfield[7] states that in a failing heart the maximum pressure approaches the minimum pressure until the pulse-pressure is *nil* and circulation ceases, and emphasizes the significance of a rising diastolic pressure. It was this article that suggested to us the use of pulse-pressure readings as a means of estimating the ability of the circulatory system to withstand strain, for it is the additional strain of the surgical ordeal that is responsible for the circulatory exhaustion or collapse in the cases cited above. Our plan was to subject the patient to the strain of work and observe not only the systolic pressures but the diastolic and pulse-pressures as well, for the pulse-pressure is the head of pressure which is actually driving the blood through the circulatory system, and inasmuch as the cardiovascular system maintains pulse-pressure when an additional strain is imposed on it, so much is efficient circulation maintained. During the course of our work a brief paper by Lankford[8] appeared in which he describes practically the same test, suggested to him by Jackson, of Rochester, which he has been using satisfactorily in life insurance examinations.

Our method of testing patients is to subject them to moderate exercise, such as the use of dumb-bells or walking rapidly for prescribed distances, depending on the nature of the case and noting the effect on the pulse-rate and the systolic, diastolic, and pulse-pressures. The auscultatory method is used for blood-pressure and the transition from the third to fourth phase is considered as diastolic pressure. The pulse-rate for one-half minute and the systolic and diastolic pressures are taken with the patient in the recumbent position. This is repeated with the patient in the standing position, and then after the exercise, and again with the patient in the recumbent position. Normally in changing from the recumbent to the upright position there is a compensatory

[5] Arch. Int. Med., November 15, 1915, 795.
[6] Deutsch. med. Wchnschr., 1906, No. 26
[7] New York Med. Jour., September 4, 1915, 508.
[8] Southern Med. Jour., March, 1916, p. 193.

response on the part of the vasomotors, so that the hydrostatic effects of gravity are overcome and circulation is maintained.

Sewall[9] emphasizes the fact that in patients with poor vasomotor tone, as is so often seen in debilitated conditions or in cases with splanchnoptosis, there is a fall in systolic pressure in changing from the recumbent to the upright position. We have found this to be true, and we find that it is necessary to take readings in the upright position previous to the exercise in order to note the true effects of the exercise on the pulse-rate and blood-pressure. By taking readings in the recumbent position also we are able to estimate the vasomotor tone of the patient. The following is an example of marked symptoms in such a case, and the chart readily explains the cause of the patient's symptoms. In this case, however, it is the fall in pulse-pressure due to rise in diastolic pressure rather than a fall in systolic pressure that produces the symptoms. There is a marked splanchnoptosis and there is retention of bismuth contents in the stomach after six hours.

CASE I.—Mrs. M. B., aged thirty-three years. Patient is confined to bed constantly because of dizziness, faintness, and exhaustion, with dyspnea, sighing respirations, and yawning when in the upright position. Patient has the same symptoms after eating or at defecation. Some relief on application of abdominal binder. Feels better when walking than when standing. Roentgen ray of bismuth meal shows large prolapsed stomach with lower border in the pelvis.

PULSE–PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	84	95	70	25
Standing	156	110	100	10
After exercise	160	112	95	17
Reclining	96	110	95	15

Note the marked increase in pulse-rate and the fall in pulse-pressure due to rise in diastolic pressure when patient is in the upright position. This was associated with a feeling of faintness and palpitation.

In the use of dumb-bells all readings are taken in the recumbent or in the upright position. Normally after moderate exercise there will be a rise or at least there should not be a fall in systolic pressure. There should also be an increase in pulse-pressure.

A fall in pulse-pressure, whether due to a fall in systolic pressure or a rise in diastolic pressure, or both, is considered as evidence of poor response to mild strain on the part of the circulatory apparatus. This is usually associated with an undue increase in pulse-rate, and is usually accompanied by breathlessness, dizziness, or fatigue. A marked fall of pulse-pressure is considered as a grave sign. It is in these cases of poor response to exercise that we are

9 AM. JOUR. MED. SC., April, 1916, p. 491.

especially cautious as to the amount of operative strain we are willing to submit the patient, and frequently to the extent of refusing operative procedures. The following cases illustrates poor response to exercise:
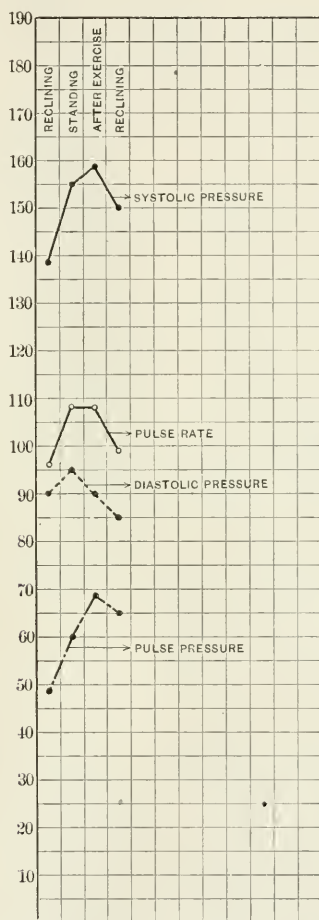
CHART I.—Normal response to exercise. Case 2, Mrs. D., aged sixty years. Two days after above test a large cyst containing 9 liters of fluid was removed from lesser peritoneal cavity by Dr. Huggins. Spinal anesthesia; good recovery.

CASE III.—Mrs. S., aged forty years. Diagnosis: Prolapse of uterus; duration ten years. Worse in last six months. Attacks of vertigo and occipital headaches, shortness of breath on exertion, and palpitation at times.

FIRST TEST ON DAY AFTER ADMISSION.

	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	118	80	38
After exercise	120	112	8

SECOND TEST AFTER TEN DAYS' REST IN HOSPITAL.

	Pulse rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	88	108	72	36
Standing	106	116	94	22
After exercise	106	106	94	12

Note fall in pulse-pressure, chiefly due to rise in diastolic pressure. Patient was refused operation at this time.
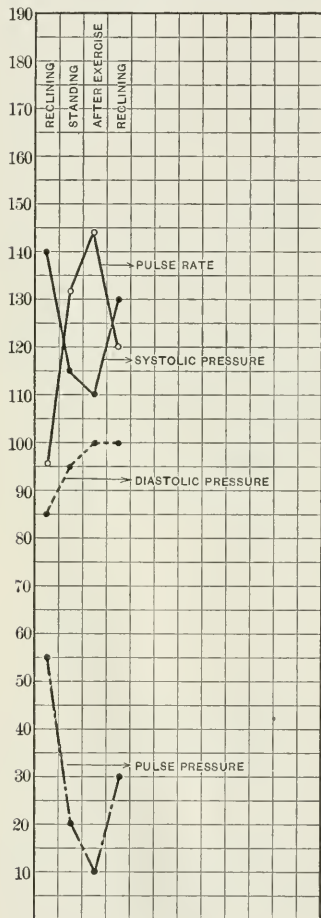
CHART II

CHART III

CHART II.—Very poor response to exercise. Case 4, Mrs. S., aged forty-eight years. Diagnosis: carcinoma of cervix. Operation: amputation of cervix, with cautery, under low spinal anesthesia. Above test was made five weeks after this operation. Patient had attacks of dyspnea at night, and at no time was it deemed advisable to undertake further operative procedures.
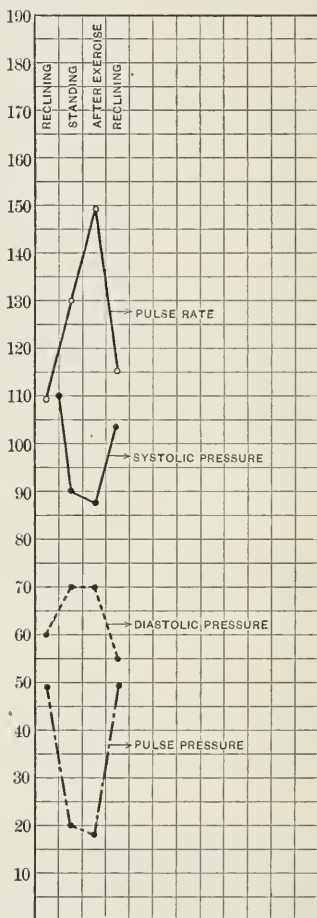
CHART III.—Very poor response to exercise. Case 5, Mrs. B., aged fifty-six years. Diagnosis: lacerated perineum. First degree prolapse of uterus. Chronic endocervicitis. Patient was kept in bed for two weeks, with very little improvement in general condition. Following operation was done under local infiltration anesthesia by Dr. Huggins: D. and C. Amputation of cervix; perineorrhaphy; good recovery.

Case VI.—Mrs. L., aged fifty-two years. Diagnosis: Lacerated cervix, chronic cystitis, and pyelitis. Chronic appendicitis, omental adhesions.

PULSE-PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	82	120	75	45
Standing	96	95	70	20
After exercise	104	95	70	25
Reclining	80	130	75	55
Reclining (ten minutes later)	..	125	70	55
After use of dumb-bells	..	108	85	23

Two weeks later the following operation was done by Dr. Huggins under spinal anesthesia: Trachelorrhaphy, appendectomy, separation of omental adhesions.

Patient suffered from distention for several days after operation. Recovery otherwise uneventful.

Case VII.—Mrs. S., aged forty-one years. Diagnosis: Bilateral chronic salpingitis with adhesions. Patient has attacks of dizziness and dyspnea on slight exertion. No swelling of feet and ankles. Heart normal in size. Point of maximum impulse in normal position. Heart sounds clear. Rate is increased above normal. Acrocyanosis present. Urine shows trace of albumin.

PULSE-PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	90	95	75	20
Standing	120	85	72	13
After exercise	144	?	?	?
Reclining	108	80	65	15

After exercise the pulse was rapid and scarcely palpable at wrist. Heart sounds were weak but no murmurs heard. Patient complained of feeling weak and faint. Face had distressed appearance. Sounds were not heard at elbow and blood-pressure readings could not be determined. Patient was refused operation.

It will be noted that in Cases III and VII the patients were refused operation. In Case IV (Chart II) an incomplete operation was performed under low spinal anesthesia. This judgment was confirmed by the after-history of this patient. Three months after she went home she was still confined to bed because of weakness and "smothering spells." In the other cases operation was done under local or spinal anesthesia in order to throw the least possible strain on the circulatory system. All of these patients gave a history of tiring easily, or slight dyspnea, or slight swelling of the feet, or dizziness or spots before the eyes, or palpitation at times. These are often not sufficient to attract the attention of the intern in taking the history, and in the routine physical

examination the heart is usually passed as normal. These patients are often well nourished and of a florid complexion, so that at first sight they appear to be good surgical risks. The increased rate and the quality of the pulse are the most important signs in attracting our attention.

The following case is of interest because the patient was sent into the hospital by her physician for observation, with diagnosis of "hysteria." Patient is a stout, red-faced woman, weighing 190 pounds. She complains of weakness and "weak spells." Four weeks ago she had a weak spell, with shortness of breath, and patient fainted. Routine examination of heart and lungs negative, except weak heart-sounds. Hemoglobin, 100 per cent. Wassermann test negative. Urine contains a trace of albumin, otherwise negative. Pulse regular but weak.

CASE VIII.—Mrs. S., aged thirty-one years.

PULSE-PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	54	90	55	35
Standing	112	85	70	15
After exercise	120	?	?	?
Reclining	54	95	65	30

After exercise the patient complained of exhaustion. The pulse was scarcely palpable at wrist and the sounds were not heard at the elbow. With patient in the upright position before the exercise the sounds at the elbow were faint on listening with the stethoscope.

In our blood-pressure observations under spinal anesthesia, difficulty has frequently been experienced in determining the diastolic pressure because of the marked lowering of pressure in this type of anesthesia, so that at present we are using a blood-pressure bracelet stethoscope for all blood-pressure observations, and this will probably eliminate the difficulties experienced in the above two cases (Cases VII and VIII) in determining the pressures after exercise.

The next case illustrates what happened after operation in a case showing poor response to the pulse-pressure test:

CASE IX.—Mrs. P. McH., aged thirty years. Admitted December 17, 1916.

Clinical Condition. Pain in abdomen.

Family History. Negative.

Past History. Rheumatism when she was young (in bed two weeks). Frequent sore throats when young. No dyspnea. No palpitation. Menstrual history negative. Married two years. No pregnancies.

Present Illness. Began one month ago with soreness in both iliac regions. Soreness gradually became worse until twelve days

ago, when she had severe sharp stabbing pains in both iliac regions.
Pains intermittent. More severe at night than in day. Pain was
worse on left side at first, but the last few days has been worse
on right side. Marked increase in leucorrhea since onset of point
impulse.

Physical Examination. Vaginal examination shows pelvis filled
with a fixed, hard, tender mass. Uterus fixed. Mass is larger on
left side. Mass apparently includes uterus and adnexa and con-
sists of inflammatory exudate. No softening nor fluctuation
made out. Temperature 100° F. White blood cells, 18,000.
Patient was kept in bed for eleven days, during which time she
complained of pounding of heart at times. Rate was accelerated.
Temperature became normal and all pain in pelvis disappeared.
Heart normal in size. Sounds clear. First sound weak and
tendency to embryocardia present. Rate 108 per minute. The
pulse-pressure test was then made, with the following results:

PULSE-PRESSURE TEST, CASE NO. 9.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	108	95	60	35
Standing	132	90	75	15
After exercise	144	88	75	13
Reclining	108	90	65	25

Patient had recurrence of pain in pelvis for a day or so after
this exercise, which again subsided. Three weeks after admission
patient was operated on by Dr. Huggins. Ether anesthesia. A
large tuboövarian abscess was found on left side and right adnexa
densely adherent. Uterus and adnexa were roofed over by adher-
ent bladder and sigmoid. Both tubes, the left ovary, and appendix
were removed and drainage established. Patient ran a very
rapid pulse throughout the operation, and pulse was weak when
patient left the table. During the first twenty-four hours the
pulse was very rapid and weak, at times being scarcely perceptible
at wrist and running between 150 and 200, as far as could be deter-
mined, after which it remained around 120 for six days and at the
present time is 110. This is the only case in which we have done
an extensive operation with ether in a patient who responded so
poorly to exercise since we began using this test, and we were
considerably alarmed as to her condition after operation and feel
that in this case the result confirmed the value of the test.

Because of the difficulties in accurately determining the blood-
pressures in cases with gross irregularities in the force of the heart-
beat this test is limited in value, but it is not in this type of case
that we need such a test, for our usual methods of examination
suffice to give us ample warning of the condition. Its chief value
is in the cases in which the force and rhythm are regular or but

slightly irregular, the type of case in which our ordinary method of examination does not throw light on the condition of the circulatory apparatus, and the type of case in which surgeons are so liable to blunder. We feel that this test signifies the ability of the cardiovascular system to respond to strain at the time the test is made and that it does not signify what portion of the cardiovascular system is at fault. The condition may be due to a permanently damaged heart muscle or cardiovascular system, which is working with very little reserve and which may fail if subjected to sudden strain. On the other hand the condition may be a temporary one, due to toxemia, exhaustion, or fatigue, but nevertheless this is the type of case that should not be subjected to additional severe strain. How frequently we find women who are worn out from multiple pregnancies, toxemias, and chronic infections suffering from chronic fatigue and exhaustion. If the histories of these patients are gone into carefully we find that they tire readily, suffer from dizziness, dyspnea on exertion, weak spells, or slight swelling of the feet and ankles, although the heart appears to be normal by the ordinary methods of examination. These are the patients who have stormy convalescence after abdominal section.

Increased pulse-rate and flabby tissues usually attract our attention on physical examination. Low blood-pressure, varicose veins, and acrocyanosis are often indicative of subnormal tissue tone. The association of this condition with prolapse of the uterus, gall-bladder disease, and fibroids is sufficient to attract attention. We have found that many of these patients improve and become fairly good surgical risks after a prolonged rest in bed, and their condition is due to fatigue, apparently, or at least this makes up a goodly portion of the handicap regardless of the secondary causes. In certain cases the damage is apparently permanent and the improvement under rest is slight. The following case illustrates the improvement that may follow a prolonged rest:

One of the surprising results of this work to us is the frequency of this condition, when one is on the lookout for it, in stout women of middle age, the type that are afflicted with gall-bladder disease, prolapse of the uterus, and fibroids, and we are convinced that many of the deaths that occur one, two, and three weeks after operation in this type of patient and are attributed to embolism and various causes are in reality due to circulatory complications, many of which could be avoided by more careful preoperative study of the patients. The cases and charts cited above are only striking examples of types which we see in varying degrees.

If the preoperative apprehension, the expenditure of energy due to rapid forced breathing, rapid pulse-rate, struggling and loss of heat and fluid as a result of the ether drive, the operative trauma and hemorrhage, and the postoperative pain and discomforts be compared to the strain of a cross-country run we have analogous

conditions. If subjected to a long cross-country run these handi-capped patients would fall from exhaustion or die. Unfortunately, under anesthesia, we can carry these patients, unable to make a
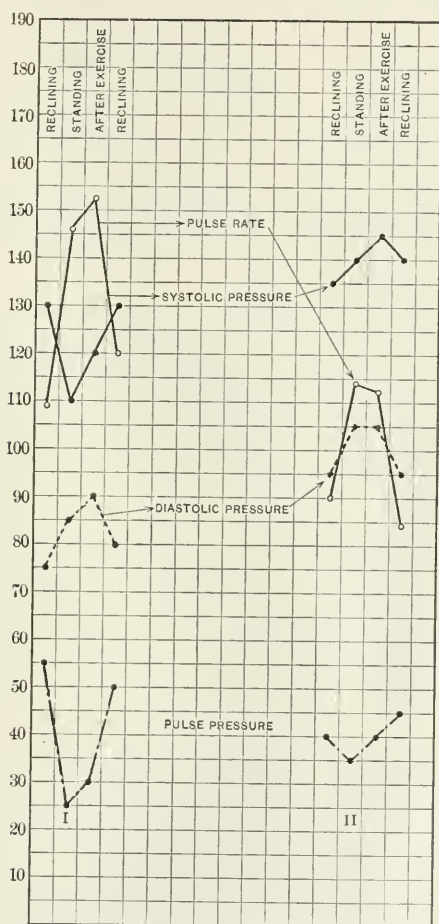
CHART IV.—Case No. 10. Mrs. M., aged forty-five years. Diagnosis: post-operative intestinal adhesions; chronic morphinism. *I*, test on first admission to hospital; *II*, test three months later, after a prolonged rest, during which patient improved in general condition. Note the improvement in pulse rate and pulse pressure curves.

protest, so far beyond the exhaustion stage that there is no come-back.

Patients with little reserve and who respond so poorly to light strain should be subjected to neither a severe operation nor a cross-country run as an elective procedure.

ACUTE APPENDICITIS: AN ANALYSIS OF 500 CASES.

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AND

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NEW YORK.

(From the Cornell University Surgical Division, Bellevue Hospital.)

THE cases forming the basis of this study were admitted to the surgical services of the first, second, and third divisions of Bellevue Hospital from the years 1911 to 1916 inclusive, and represents the work of many different surgeons.

These cases were carefully collected, including only those in which the evidence of acute inflammation of the appendix was satisfactory. We thus found it necessary to reject about one-third of the cases filed as acute appendicitis, as the data was not sufficiently conclusive to class them as such. Pathological examination was not recorded in many of the cases, but a definite judgment could be formed upon the clinical picture and the gross appearance of the appendix and surrounding tissues.

It was our experience that if the gross appearance of the appendix was not evidently that of acute disease, there was seldom other sufficient evidence to so regard it. We did not find in these records satisfactory evidence of such an entity as the often-named acute catarrhal appendicitis, and have rejected, to the disparagement of our mortality figures, many of the cases which would have gone into this class. To substantiate these views we quote from Moschcowitz:

"To recognize that an appendix is diseased or normal, the microscope . . . is by no means always necessary. I believe that in 90 per cent. the diagnosis of a present or previous appendicitis may be easily recognized by the naked eye.

"I emphasize the appearance of a localized appendicular peritonitis because it is not generally appreciated that a local peritonitis is already present in the early stages of the disease. I have never seen an appendix acutely inflamed that did not show this lesion, although I confess that I do not recall ever having examined an appendix removed in the first twelve hours after the onset of the symptoms. Without any further evidence, therefore, the absence, even grossly, of a localized appendicular peritonitis practically excludes an acute appendicitis . . . The lesion of acute appendicitis is not a catarrhal inflammation as understood in the pathological sense. Indeed, acute and even chronic inflammations of the appendix do not occur."

Stanton says: "Catarrhal appendicitis is not found as a primary

condition," and quotes from Kocher as saying: "I see appendicitis catarrhalis only as a chronic form and as a residue after acute attacks."

We propose first to discuss the mortality and complications and then such diagnostic and prognostic features of interest as may be gathered from the data collected.

MORTALITY. There were 34 deaths, or a mortality of 6.8 per cent. The accompanying table is a compilation of some report selected from the literature of acute appendicitis. In considering them it must be remembered that those that run back ten to fifteen years, as that from Mt. Sinai Hospital, antedate in part the employment of the Murphy drip and Fowler position, the introduction of which have considerably reduced the mortality in severe cases.

	No. of cases.	Died.	Mortality (per cent.).
Bellevue Hospital, 1911–1916	500	34	6.8
Roosevelt Hospital, 1910–1915 (Stillman) . .	965	46	4.7
Presbyterian Hospital, 1906–1909 (McWilliams)	687	68	9.8
Mt. Sinai Hospital, 1899–1906 (Moschcowitz) .	1,503	202	13.4
Schnitzler	937	98	10.5
Kummell (German Surgical Congress, 1910) .	574	11	2.0
Zander	308	30	9.7
Zahradnicky	641	35	5.4
All Berlin Hospitals, 1907 (from McWilliams) .	1,344	197	14.6
Syms, 1906–1912	106	8	7.5
Burgass, 1906–1911	500	40	8.0
Denk, 1907–1911	467	29	6.2
Davis	260	15	5.75
Haggard	265	12	4.5
DeQuervain, 1908–1913	5,097	417	8.1
Total	14,154	1,242	8.7

These figures demonstrate the seriousness of acute appendicitis. The most impressive study in this connection is, however, the relation of time of operation to mortality. From a condition whose death rate is approximately that of typhoid fever the disease reduces itself to one with a mortality of only 1 per cent. if operation is done within the first twenty-four hours. By the end of the second day the mortality has quadrupled, although still considerably below the general average. By the end of the third day the mortality has passed far above the general average—almost as high a figure as is attained at any time. The lesson of this is that in the presence of virulent infections and low resistance a delay of seventy-two hours seriously compromises the hope of recovery. The operation done later than twenty-four hours after the onset of symptoms cannot be considered early. It is of interest to note that of the fatal cases in this series, twice as many died who were operated upon the third day after the onset of symptoms as on any other day of the illness. The accompanying table includes the cases in which the time of operation was known:

Day of illness operated upon.	Number of cases.	Deaths.	Mortality (per cent.).
First	111	1	0.9
Second	109	4	4.0
Third	89	10	11.0
Fourth	60	5	8.0
Fifth	39	5	13.0
Sixth and seventh	33	4	12.0
Second week	33	3	9.0
More than two weeks	13		

Figures from other clinics in general agree with ours. McWilliams' statistics from the Presbyterian Hospital, New York City are:

BEEKMAN, SMITH AND EVERINGHAM
MC WILLIAMS
BERLIN MEDICAL SOCIETY
DE QUERVAIN
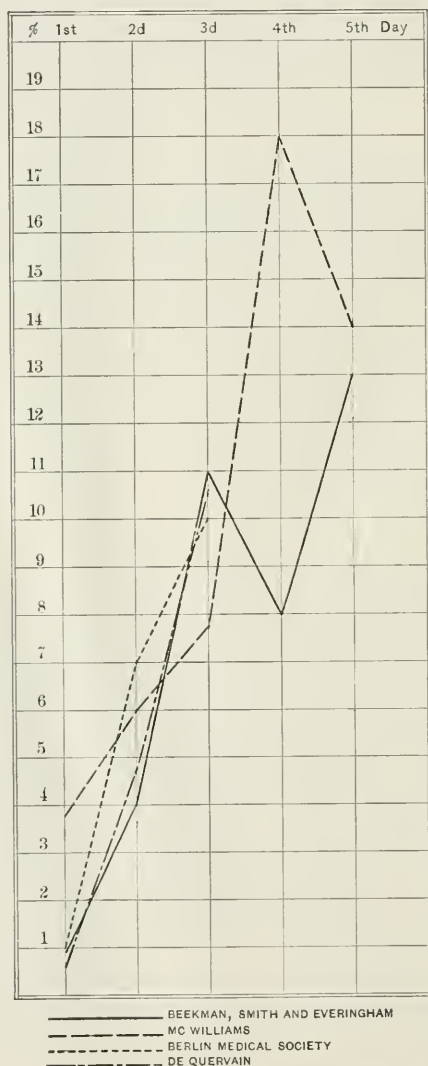
The rate of mortality in acute appendicitis in reference to the day of the attack on which the operation is performed.

Day of illness operated upon.	Mortality (per cent.).
First	3.7
Second	6.0
Third	7.7
Fourth	18.0
Fifth	14.0
Sixth	14.0
Seventh	20.8
Seventh to tenth	20.0
Tenth to fourteenth	15.3

A Commission of the Berlin Medical Society for Berlin Hospitals, 1907, report as follows:

Day of illness operated upon.	Mortality (per cent.).
First	0.9
Second	7.0
Third	10.0
Later	23.0

De Quervain's report from the Swiss Hospitals, 1908 to 1913, gives us the following, from 5097 cases:

Day of illness operated upon.	Mortality (per cent.).
First	0.69
Second	4.7
Third	10.7
Later	21.2

Another factor influencing mortality is the age of the patient; the very young and the elderly often succumb. In this series the mortality of those under ten years and over fifty is 23 per cent. as opposed to a mortality of 4.7 per cent. for those between. This increase in mortality in the young and old is confirmed by studying the following table, which gives the mortality of the young and old, depending upon the day of the attack on which operation was performed, compared with those of the whole series:

Day of illness operated upon.	Mortality of series, 500 cases (per cent.).	Mortality of young and aged (per cent.).
First	0.9	0.0
Second	4.0	31.0
Third	11.0	25.0
Fourth	8.0	33.0
Fifth	13.0	33.0

The causes of death in our series of cases were:

Diffuse peritonitis	18
Diffuse peritonitis with left iliac phlebitis and pleurisy	1
Diffuse peritonitis with multiple liver abscesses and pleurisy	1
Diffuse peritonitis with pneumonia	1
Prolonged sepsis and fecal fistula	3
Sepsis	1
Septicemia and pneumonia	1
Subphrenic abscesses	2
Pneumonia	3
Pulmonary embolism	1
Alcoholism	1
Facial erysipelas	1
	34

COMPLICATIONS. These may be divided into two classes, complications already present at time of operation and postoperative sequelæ. The complications already present at operation were:

Complication.	Incidence (per cent.).	Cases.	Mortality (per cent.).
Abscess	21.0	107	5.6
Diffuse peritonitis	9.0	45	47.0
Tuboövarian abscess	0.4	2	
Acute cholecystitis (suppurative)	0.4	2	50.0
Obstruction due to adhesions	0.2	1	
Salpingitis	0.2	1	
Toxemia of pregnancy	0.2	1	100.0
Alcoholism	0.2	1	100.0
Pulmonary tuberculosis	0.2	1	100.0
Nephritis	0.2	1	100.0

These complications were found in 151 individuals, or 30 per cent. The mortalities here quoted do not necessarily represent the mortality of a given complication, as more than one complication often existed in the same individual. For instance, in the cases dying in which pulmonary tuberculosis and nephritis were quoted as complications there was in addition diffuse peritonitis.

Abscess. There were 107 cases of appendicular abscess, or 21 per cent. of the total cases studied. The mortality was 5.7 per cent. (6 deaths), a little better than the general mortality. The causes of death were diffuse peritonitis 4, pneumonia 1, and erysipelas 1. The incidence of other complications was approximately that of the whole series. Fecal fistula occurred relatively more frequently, 8 times. This is perhaps due to the fact that in 18 of these cases or 17 per cent., the appendix was not removed. Abscess should occur in only a small percentage of cases promptly operated upon, less than 3 per cent. the first day as opposed to over 50 per cent. in those delaying beyond the fourth day. The following table demonstrates this fact:

Cases operated upon.	Days ill.	Abscesses found.	Incidence (per cent.).
111	1	3	2.7
109	2	16	15.0
89	3	11	12.0
60	4	12	˙20.0
39	5	18	46.0
33	6 and 7	17	51.0
33	2d week	20	60.0
13 more than 2 weeks		9	69.0

Diffuse Peritonitis. There were 45 instances, or 9 per cent., of this serious complication of the series. Many cases which had a pelvic peritonitis are excluded from this list, as our endeavor is to include only such as had a widespread peritonitis, the class usually designated in the histories as general peritonitis. Twenty-one, or 47 per cent., of these cases died, more than half the total fatalities. A number of them were further complicated. The importance of the time element in operative interference is here again forcibly illus-

trated.   In the fatal cases the average time of illness before opera-
tion was nearly double that of the cases recovering, 4.7 as opposed
to 2.5 days.   Of the 12 cases with diffuse peritonitis not more than
two days ill before operation, not one died.   Of the fatal cases only
6 of the 21 lived longer than five days after operation, the majority
succumbing before the end of the third day.

Acute suppurative cholecystitis was twice found at operation
coincident with acute appendicitis.   One of these cases in which a
diffuse peritonitis was a further complication died.   The other
recovered.

The postoperative sequalæ were as follows:

Sequelæ.	Incidence	Cases.	Mortality.
Fecal fistula	5.0	24	17
Pneumonia	2.5	12	33
Infected wounds in undrained cases	2.5	12	
Secondary peritoneal abscess, including three subphrenic	2.0	10	40
Pleurisy (one suppurative)	0.6	3	66
Phlebitis	0.4	2	50
Early ventral hernia	0.4	2	50
Facial erysipelas	0.4	2	50
Tonsillitis	0.4	2	
Rheumatism	0.4	2	
Alveolar abscess	0.4	2	
Pulmonary embolism	0.2	1	100
Septicemia	0.2	1	100
Ileus paralytic (operated)	0.2	1	
Liver abscesses	0.2	1	100
Parotitis	0.2	1	.
Bronchitis	0.2	1	
Pulmonary edema (slight)	0.2	1	
Abscess of neck	0.2	1	
Acute mania	0.2	1	

Here, again, it must be remembered that the mortality quoted
does not necessarily represent that of the complication alone.

Fecal Fistula.   Fecal fistula occurred 24 times in the series, an
incidence of 5 per cent.; 4 died, a mortality of 17 per cent.   Fistula
alone is not in itself a serious menace to the life of a patient.   All
but one of the fecal fistula cases were drainage cases.   In 22 cases
in which we have compiled fuller data the following facts are of
interest: In 14 cases the base of the appendix was ligated only, in
4 it was inverted, in 1 the caput coli was resected, and in 3 cases the
appendix was not removed.   The advantage of invertion of the
stump over simple ligation, as regards the formation of fecal fistula
may be only apparent, since data concerning the cecal wall is want-
ing.   The outcome of these cases as fully as it could be obtained
from the histories was:

Spontaneous closure of the fistula	12
Discharged with fistula still open (two patients left against advice)	4
Operative closure of fistula	2
Died, fistula still open (one case secondarily operated upon)	4

Of the 18 surviving cases, 12, or 66 per cent., closed spontaneously, and it is fair to assume that others of the 4 discharged, with fistulæ draining, closed later without operation. Stillman, in reviewing the cases of appendicitis at the Roosevelt Hospital for the years 1910–1915, reports 64 per cent. of spontaneous cures of this condition. The incident of fecal fistula in this series is decidedly higher than in the Roosevelt Hospital series or the Presbyterian Hospital series reported by McWilliams. In this connection it is of interest to note that in our series, where the treatment of the stump is known, it was ligated in 245 cases and inverted in 196. Incidence of fistula is 5.7 per cent. in the ligated cases as opposed to 2 per cent. in the inverted.

Pneumonia. Pneumonia occurred 12 times, an incidence of 2.5 per cent. In 3 cases it was the only complication, and all of these survived. There were 4 fatalities in the series, or 33 per cent. It is fair to assume therefore that pneumonia will occur less frequently in those upon whom an early operation is performed, and there will consequently be less risk to the patient.

Secondary Abscess. Secondary peritoneal abscess occurred in 11 instances, being present in 1 case at operation and 10 times as a sequela. Three of these were subphrenic abscesses. Of the 11 cases, 4 died, a mortality of 36 per cent. Two of these deaths occurred in patients with subphrenic abscesses, a third in a patient who had septicemia, and a fourth in a patient with fecal fistula. In the Roosevelt Hospital cases this was the most frequent sequel, whereas in this series both fecal fistula and pneumonia occurred more often.

Ileus. This series is remarkable for the small number of cases of ileus, there being only 2. In 1 it was found at operation due to adhesions. A secondary operation was done on the second case, but the condition found was that of a paralytic ileus. Both cases recovered. In the Presbyterian Hospital series reported by McWilliams there were 18 cases of ileus out of a series of 687 cases of acute appendicitis, 14 paralytic and 4 mechanical obstructions, with 14 deaths; and in the Roosevelt series reported by Stillman there were 13 cases out of 965 operated upon for acute appendicitis, with 8 deaths.

It must be assumed, however, that some of our cases of diffuse peritonitis had a paralytic ileus, and therefore the above statistics may be misleading.

DIAGNOSIS AND PROGNOSIS. Some facts of interest from the stand-point of diagnosis and prognosis follow.

Previous Attacks. A history of previous attacks was obtained in one-fourth of the cases. Other writers have reported a great incidence of previous attacks, undoubtedly the more painstaking the historian the greater number of such previous facts in the history will be obtained.

Season of the Year. The question of seasonable variation was studied. The only deduction to be made is that season exercises no dominating effect.

Sex. The number of males in this series was a little more than twice that of females, while male deaths were relatively slightly less frequent; other writers agree to the preponderence of males in acute cases.

SYMPTOMS. *Vomiting.* Vomiting is a very constant symptom in acute appendicitis and is mentioned in the histories of four-fifths of the cases of this series. Five per cent. more had nausea without vomiting.

Constipation. When the condition of the bowels was recorded, constipation was five times as frequent as diarrhea.

Temperature. Acute appendicitis is characterized by moderate temperatures, although a normal temperature or high one does not preclude this diagnosis. Very high temperatures were followed by a higher mortality than the average; this is usually due, however, to an accompanying diffuse peritonitis, as may be seen from the following: there were 16 cases with a temperature over 104°, 10 of which had a diffuse peritonitis, the mortality being 25 per cent. The subsequent mortality in those cases with normal temperature at operation was approximately the average.

Temperature.	No. cases.	Subsequent deaths.	Mortality (per cent.).
Under 99°	33	2	6.2
99° to 100°	101	6	5.9
100° to 101°	130	3	2.3
101° to 102°	111	11	10.0
102° to 103°	68	4	5.9
103° to 104°	39	4	11.0
104° plus	16	4	25.0

Pulse. Pulse-rate seems to be of more significance than temperature from a prognostic stand-point, yet each individual case must be judged on its own merits. The accompanying figures summarize the facts:

Pulse at operation.	Percentage of cases.	Subsequent mortality.
Under 100	45	3.6
100 to 120	31	8.3
120 and over	23	11.0

Of the cases of diffuse peritonitis, four-fifths had a pulse of 100 or more at operation, and of the remaining one-fifth the majority were between 95 and 100.

Blood Count. A blood count was recorded in 377 of the cases. Neither a normal blood count nor a very high one rules out appendicitis, although such counts are comparatively rare. The mortality was higher among the two extremes and most favorable with a moderate leukocytoses. The relation of the numerical count to

the differential, as suggested by Gibson, did not appear to give any prognostic significance among our cases.

Blood count.	No. of cases.	Incidence (per cent.)	Mortality. (per cent.)
10,000 or under	22	6.0	14.0
11,000 to 15,000	119	31.0	6.0
16,000 to 20,000	113	30.0	5.0
21,000 to 25,000	69	18.0	9.0
26,000 to 30,000	28	7.0	11.0
31,000 plus	26	7.0	15.0

The average polynuclear count was 85 per cent.
With 80 per cent. or less polynuclears the mortality was 4 per cent.
With 80 to 89 per cent. polynuclears the mortality was 6 per cent.
With 90 plus per cent. polynuclears the mortality was 14 per cent.

The importance of early operation in regard to prognosis has been sufficiently dwelt upon under the discussion of mortality and diffuse peritonitis. It is important to add a table showing the duration of hospital stay with reference to time of operation. This emphasizes the fact that early operation is not only life-saving but time-saving.

Days ill at time of operation.	Average hospital stay.
One-half	13.1 days
One	16.7 "
Two	21.8 "
Three	21.7 "
Four and five	23.3 "
Six and more	25.2 "

Age. The relation of age to prognosis is important, as has already been brought out in discussing mortality; 87 per cent. of the cases in this series were between the ages of ten and fifty, with a mortality of 4.7 per cent., as opposed to a mortality of 23 per cent. in those at the two extremes. The accompanying table gives the figures:

Ages by decades.	No. of cases.	Deaths.	Mortality (per cent.).
1 to 9	42	7	16.0
10 to 19	158	2	1.2
20 to 29	174	12	6.9
30 to 39	62	3	4.8
40 to 49	36	3	8.3
50 plus	24	8	33.0

CONDITION OF THE APPENDIX. The cases were finely studied with a view of determining how much information of a prognostic nature could be derived from the condition of the appendix at operation. In 435 of the cases a division into three classes, suppurative, gangrenous without perforation, and perforative, was made. It is clearly recognized that these are different degrees of the same process, yet they represent the progress of the disease. Of course, the chief element in judging the outcome, when the surgeon lookes into the abdomen, is the spread of the inflammation, yet it is thought that this tabulation may add something of interest:

Of the 117 perforated cases 17 died, a mortality of 15 per cent.

Of the 138 cases with gangrene and no perforation 9 died, a mortality of 6.5 per cent.

Of 180 suppurative cases without either perforation or gangrene 4 died, a mortality of 2 per cent.

Thirty per cent. of perforated, 16 per cent. of gangrenous and 10 per cent. of suppurative cases developed abscesses.

Twenty-four per cent. of perforated, 8 per cent. of gangrenous, and 1 per cent. of suppurative developed diffuse peritonitis.

The incidence of all complications in perforative cases is 61 per cent., in gangrenous 38 per cent., and in suppurative 22 per cent.

It appears from this that the danger of a diffuse peritonitis is greater when there is a perforation than when the inflammation spreads through the appendicular wall, for in the latter case there is a better chance of the peritoneum localizing the disease.

There were 20 cases, or 4 per cent., in whom it was not possible to remove the appendix. All but two of these were in abscess cases. Three of the 20 died, a mortality of 15 per cent.

SUMMARY. The mortality in our series of acute appendicitis cases was 6.8 per cent. We believe that this mortality figure may be greatly improved by making an early diagnosis followed by immediate operation, as we have shown that the mortality of those operated upon during the first day is less than 1 per cent., whereas by the third day it is over 10 per cent.

The mortality is higher in the young than in the old.

Death can be ascribed to intra-abdominal suppuration in 82 per cent. of our 34 fatal cases; of these 21, or 62 per cent., it was due to a diffuse peritonitis.

A temperature over 104° is usually indicative of diffuse peritonitis.

Abscess was found to be present in 21 per cent. while diffuse peritonitis was found in but 9 per cent., however, the mortality of the former was but 5.6 per cent. compared with 47 per cent. of the latter.

In the fatal cases of diffuse peritonitis the average time of the illness before operation was nearly double that of the cases recovering. Moreover, in 12 cases suffering from diffuse peritonitis and operated upon within forty-eight hours, there was no mortality.

Fecal fistula and postoperative pneumonia were the most common sequelæ, the former in 5 per cent. the latter in 2.5 per cent.

We feel that it is impossible to make a diagnosis from the symptoms present, a severe case often showing the least marked signs.

In conclusion, we wish to emphasize the fact that operation should should be performed as soon as the diagnosis of appendicitis is made, for the shorter the period between the onset of the disease and surgical interference the better the prognosis; the death rate being lower, few complications and sequelæ developing, and the stay in the hospital shortened.

We wish to acknowledge our thanks to the surgeons of the first,

second, and third divisions of Bellevue Hospital for allowing us to use their records and to Dr. John A. Hartwell, director of the Cornell University Surgical Division, Bellevue Hospital, for his advice and help in writing this report.

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TWO CASES OF CONGENITAL PERSISTENT ACROASPHYXIA IN INFANTS.

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THE following seem to be two cases of acroasphyxia (acrocyanosis), a local vasomotor disturbance usually symmetrical and confined to the extremities. Its pathogenesis is not known, but it is much like Raynaud's disease, of which it may be a form. It must be distinguished from acroparesthesia, erythromelalgia, multiple gangrene, scleroderma, acromegaly, and local cyanosis due to vasomotor paralysis (hemiplegia, etc.), pulmonary disease, or organic change in the arteries, such as stenosis of the aorta or thromb-angiitis obliterans. The disease was first described by Nothnagel in 1867, and since then about 35 cases have been reported. An hypertrophic form (edematous) and a hypesthetic form are usually recognized, but hypesthesia and hypertrophy may be absent. The disease occurs most frequently in girls and young women. My cases are the youngest reported. The disease has no hereditary basis, but several cases have been reported in hysterical individuals. The condition is said to be made worse by local chilling and possibly

by fatigue and dampness. The course of the disease consists of a gradually developing asphyxia which may be persistent or alternate with ischemia or active hyperemia. Gangrene occasionally results. Edema and possibly hypesthesia are probably secondary to the altered local metabolism produced by the cyanosis.

My first case was seen at the Washington University Children's Dispensary on two occasions only, and time did not permit an extended study. The second case was studied at the Garrett Hospital for Children, Baltimore, Md. All special examinations were repeated several times over a period of three weeks. I have preserved the case records of 1100 sick children, but I have seen as many more. The ratio of one case of acroasphyxia to 1100 unselected cases is about that given by Osler as the frequency of Raynaud's disease at the Johns Hopkins Hospital. The disease is probably not as rare as indicated by the scanty literature.

Case I.—*History.* No evidence of nervous, mental, or vasomotor disturbances in the family. Parents young and normal. No symptoms of syphilis or rheumatism, etc. No miscarriages. Baby, full term, is last of three children, the other two being normal. Labor was short and easy; baby cried at birth and was thought not to have been cyanotic. Took breast readily, held head up at two months, and sat up at four months(?). Laughs and sleeps normally; uses limbs normally. Nursed about every two hours the first seven months, then on condensed milk and crackers. Only illness was constipation, beginning five weeks ago, which improved after regulation of diet. No snuffles, bronchitis, etc.

Condition in feet and hands was first noticed in the baby's second week. It has gradually become worse, but was first thought to be nothing more than an increased liability to cold hands and feet. Up to two or three months ago feet and hands could be brought very near to normal appearance by keeping them warm, but since then this has not been kept up, as it was recognized that local cyanosis was no longer amenable to warmth. The asphyxia has not made the baby cry more than usual. The lesions developed synchronously in hands and feet and to equal extent over the areas involved. The extent of asphyxia has not noticeably increased during the past half-year. The earliest lesion may have been an ischemia, as the toes and the soles of the feet were white when the baby was two and three weeks old. The past eight months the cyanosis has been deepening, but does not seem to have increased the coldness of the areas, which was always marked.

Physical Examination. Negress, nine months old. Weight and build normal. Panniculus and tissue turgor normal. Skin warm, moist, and elastic; no lesions except local cyanosis in hands and feet. No glandular enlargement. Temperature, pulse, and respiration normal. Slight curly black hair. Sutures and fontanels closed except the anterior, which measured about 1 x 1.5 cm. No

craniotabes or bosses. No aural or nasal discharge. Pupils react to light; is said to have a convergent strabismus at times; no nystagmus. Mucous membranes good color, no lesions; tongue of normal size and color, no coat. Incisors present. Tonsils normal; adenoids not enlarged. Neck and thorax normal. No rosary or kyphosis. Respiratory excursion good; scant coarse rales over both lungs, but no evidence of consolidation. Cardiac dulness not increased; rhythm and sounds normal, no murmurs heard. Abdomen ovoid, slightly above costal angle, flaccid and not tender. No visible peristalsis. Spleen not palpable. Liver below costal margin in midclavicular line. Inguinal canals, anus, and genitalia normal. A light clear urine was passed during the examination, but could not be caught for analysis. Extremities showed no bone, epiphyseal, or joint lesions. Nails normal. Crawls only. Abdominal and patellar reflexes active and equal on the two sides. No Babinski or Kernig. Reacts to pin-prick.

The temperature and color of the skin is normal except in the hands and the feet, where there is marked cyanosis and coldness of the skin not caused by inclement weather. The cyanosis is equal on the two sides, and is uniformly distributed from finger-tips to carpal furrow of wrist, the light greenish-black color fading rather abruptly in an irregular line into the normal café au lait skin. In the feet the cyanosis extends over the planter surfaces to the malleoli and up to the insertions of the tendines calcanei, but only half-way up the dorsal surface of the feet. In the latter places the cyanosis fades off gradually. The area is not dry but is quite cold. Pulsation in the dorsalis pedis was not looked for. No trophic or inflammatory change could be made out. Pressure over the involved area caused an anemia that was only slowly replaced by the usual congestion. There was no local edema, and the involved area was not raised. No telangiectasis.

CASE II.—*History.* Nervous, mental, vasomotor disturbances and other diseases in the family were denied. Parents, in middle life, are both well. No evidence of syphilis, rheumatism, tuberculosis, cardiac, or renal disease. No miscarriages. Baby was the last of ten children, seven of whom are healthy and normal. The third and seventh children died in infancy of pneumonia. The baby was full term and weighed seven pounds; the labor was normal in length but easy. The baby was not cyanosed, breathed spontaneously, and has had no convulsions. It held its head up at three months and sat up at about five and a half months. Laughs, sleeps, and uses limbs normally. Does not crawl. Nursed regularly every three hours the first three months. Weaned on account of milk failing. Since then has been getting 2 ounces of unboiled milk, 2 ounces of boiled water, and 1 teaspoonful of lactose every three or four hours. No other food. There have been no traumatisms. Except for the acroasphyxia it was a healthy and quiet

baby up to three weeks ago (six months of age), when it had a moderate bronchitis and a diarrhea which lasted three weeks. Had always gained in weight up to three weeks ago. Was brought to dispensary because it was not gaining in weight, and was having curds in stools.

The cyanosis of the hands and feet was first noticed on the second day after birth; it was slight, and no attention was paid to it until it had persisted for a week or so. There was no initial ischemia, but always a congestion and cyanosis that has not increased in extent or intensity. The cyanosis would become increased when the hands or feet were exposed to the cold. When warmed the dark blue would give place to a deep mulberry color. The mother said that the hands and feet were generally darker in the early morning than at other times, but thought it was due to their not having been kept warm enough during the night. The asphyxia was always of the same intensity in all of the four extremities. There were distinct remissions in the asphyxia. Once or twice it nearly disappeared without the use of local heat, but these remissions lasted only for a few days; they could not be attributed to any cause, but a diarrhea would cause a slight fading of the lesion.

Physical Examination. Well-developed and nourished white female, aged seven months, weighing 20 pounds. Normal frame and musculature. Panniculus good. Tissue turgor and skin normal. No general glandular enlargement. Temperature, pulse, respiration, when asleep, normal. Occasional dry cough. Full, rosy-cheeked, smiling face. Attention held readily; reaches for rattle. Moves freely in bed, using all muscles normally. Erector spini not weak. Head normal in size and shape. Sutures and posterior fontanel closed. Anterior fontanel measured 2 x 2.5 cm. No bosses, craniotabes, or head sweating. Left ear normal. Right ear showed bulging drum, which was incised and ear discharged for ten days; no mastoid edema or tenderness. Nose and posterior nares free; no discharge; slight adenoids. Buccal and pharyngeal mucous membranes normal. Tongue clean; no thrush. Palate normal. Two lower middle incisors present and normal. Negative cultures for diphtheria organisms. No enophthalmos. Pupils round and equal, react actively to light, direct and consensually; no hippus; media clear; fundi normal, but globes seemed myoptic. Neck normal. No vertebral pain, kyphosis, or scoliosis. Thorax normal in size and shape; no rosary or grooving. Breathing quiet abdominal, equal in the two sides. No thymic dulness. Percussion note hyperresonant to bases. Breath sounds normal, occasionally wheezing. Infrequent sibilant and sonorous rales scattered over both lungs. Apex impulse palpable in middle line at fourth interspace; no thrill palpable. No cardiac dulness to right of sternum could be purcussed. Left cardiac outline normal. Muscle sounds were of good quality and none were accentuated. There

were no murmurs. Pulse at brachials synchronous and equal; volume and tension not abnormal. Abdomen level with costal cartilages, soft, not tender. No masses or deep tenderness. Spleen not palpable; liver not enlarged. Umbilicus normal. No local bulging. Inguinal canals, anus, and genitalia normal. Vaginal smear showed no gonococci. Extremities symmetrical of normal length and proportions. No epiphysitis, bone, or joint symptoms. No paresis or limitation of motion. Reflexes: triceps not elicitable; biceps slight but equal on the two sides. Abdominal reflexes active and equal. Knee-jerks equal but not active. No clonus; Oppenheim present on both sides. Testing for Babinski caused plantar flexion and withdrawal of foot. No dribbling of feces or urine; evacuations of normal quantity and frequency. Muscle tone everywhere normal; there was no local atrophy, fibrillation, tremors, or spasmodic movements. Cotton wool and finger touched to any part of body always attracted attention. Pin-prick and extremes of temperature caused pain response except when touched to cyanotic areas where there was apparently much diminished pain and temperature sensation, but *no definite hypesthesia.*

Urine, twenty-four hour catheterized specimens, showed no abnormalties by usual tests.

Stools loose, golden, streaked with green and casein curds; slight mucus and fetor; no blood.

Spinal fluid clear, no cells or ketones; Fehling's solution not reduced; Noguchi negative; trace of albumin; Wassermann negative.

Blood.	From normal areas.	From areas of asphyxia.
Flow	Normal	Scanty and only after deep incision.
Clotting time	4 to 6 minutes	Four minutes.
Specific gravity	1.058	1.060
Color	Slightly venous	Dark bluish red.
Hemoglobin	65 per cent.	65 per cent.
Platelets	About normal	Number nearly doubled.
Shape and size of red blood cells .	Normal	Normal.
Number of red blood cells . .	4,515,000	4,700,000.
Number of white blood cells . .	14,200	11,800.
Polymorphonuclears	42.3 per cent.	27.0 per cent.
Lymphocytes	55.4 "	68.0 "
Mononuclear leukocytes . . .	1.8 "	3.5 "
Eosinophiles	0.5 "	1.5 "

Blood-pressure.	Systolic.	Diastolic.
Middle of arm	80	45
Middle of forearm	65	35
Middle of thigh	70	40
Middle of leg	42	?

Local temperature (taken at room temperature of 78°) averaged:

	Rectum.	Armpit.	Hand.	Popliteal.	Feet.
	98.8	95.8	81 to 82	89.6	73 to 75
The normal being	. . .	94		92	91

Wassermann, against three antigens, negative.

Description of Lesion. Symmetrically distributed and of equal intensity over both hands and feet. The asphyxia involved the

whole hand to the wrist at the level of the styloid processes. The feet likewise were completely involved, the lesion extending up the dorsum to the level of the annular ligament and up the plantar surface to the malleoli, except that when the legs were chilled the cyanosis would extend irregularly up to the distal angle of the popliteal space. Except for the last-named extension the outlines of the lesions were constant and fairly definite as the borders faded rather abruptly. The only infiltration in the skin was on the dorsal surfaces of the hands and feet, where there was a slight edema seemingly in the cutis vera. Otherwise the lesions were not raised. The asphyxia did not give an appearance of marbling but was of a uniform deep bluish-purple bluish when the extremities were cold or was of a dark mulberry color when they were warm. For two days it faded to an old rose color, during which time the edema was not palpable. The skin was moist and no trophic changes were determinable. There was no increased perspiring in the involved areas. The pulsations in the dorsalis pedis arteries were normal. Pressure over the cyanotic areas caused a long persistent blanching that was only very slowly replaced by the capillary congestion. Stroking the hands or feet with a match caused no tâche or wheal.

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THE ANXIETY NEUROSES.[1]

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THE syndrome which is mostly discussed under the names of "precordial anxiety" and "anxiety neurosis" may be said to be two-sided, *i. e.*, to have, in a sense, a psychic and somatic side. It consists of pain, distress, or paresthesia of some kind, generally starting in the chest or epigastric region, often becoming precordial; this followed by or associated with more or less insistent anxiety or even unreasoning fear and dread or anguish, according to the severity of the condition or the intensity of the attack.

I see no difficulty in recognizing in these phenomena a distinct and fundamental type of reaction. My reasons for this view I will cite further on.

It is not only attractive but profitable to keep distinctly in view the features of this syndrome, and in attempts at an analysis of our cases to pick out the possible psychic and physical elements in each one. It seems to me that writers have failed largely to put sufficient stress on this point. We see the exaggerated forms of the syndrome discussed in connection with hypochondriasis, manic-depressive disease, and other psychoses, whereas there are many little cases, light forms, perfectly well defined, cases which are often not really or deeply complicated with other neuroses. These cases merit much attention.

We are reminded, and properly so, that sufferers of this kind must be managed from the psychic side, but it is equally true that many of them must be improved in their organic functions before psychic assistance is effective. The exposure to this type of neurotic reaction is not exactly the same in all of its subjects. We find ourselves inclined to fancy it more peripherad in one instance, more centrad in another. This conception is quite in harmony with the modern physiological interpretation of the nervous system, namely, the integrative action of reflexes. If, for illustration, we employ a simplified physiological formula to assist us in gaining this conception, the "receptor"[2] apparatus would, in this instance, carry stimuli, possibly, from cardiac, gastric, pulmonary, and skin sources to the "analyser,"[3] the central apparatus, especially prepared to receive them. Of course, it would not be physiological to speak of the receptor and the analyser as separate organs, in that to perform at all they must act as a unit, yet they are anatomical parts of a physiological unit, and we can conceive of one part in a better or a worse condition for functioning than another. And, incidentally,

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[1] Read before the St. Louis Neurological Society.
[2] Sherrington.   [3] Pawlow.

we can conceive of variation in function corresponding to the manner of crippling in some of the numerous and various units entering into a symptom-complex of the magnitude of the one under consideration.

Some years ago Krafft-Ebing wrote as follows concerning precordial anxiety:[4] "The first point to determine is the interrelation of the two phenomena. Is it possible that these paraplegic sensations in the epigastrium are the expression of a primary excitation of sensory nerves, this state of excitement being conducted to consciousness and there inducing a feeling of anxiety? or it may be that for the psychic process they are simultaneous and coördinated states of excitation in the central sensory nerves, this excitement, according to the law of excentric projection, being carried to the peripheral ends of the conducting path."

"Precordial anxiety, as experience teaches, may be induced by psychic stimuli, such as frightful ideas, apperceptions, and emotions, and thus it may be of central origin; or it may be caused by neuralgias, and thus be of peripheral origin. The peripheral manner of origin is to be explained only by irradiation of a sensory stimulus to the nervous system of the heart." In this quotation Krafft-Ebing clearly recognizes that the emotions are primarily and chiefly concerned in the psychic side of this problem. He also hints at the relation of the vasomotor system to the syndrome, and he is evidently interested in the question of the peripheral origin of it.

In order to consider these three items a little further from a physiological stand-point I will introduce some citations from a more recent author. Having in mind the difficulty of reconciling certain psychological problems with modern physiological deductions, Sherrington[5] says: "Of points where physiology and psychology touch the place of one lies at 'emotion.'

"Built upon sense-feeling much as cognition is built on sense-perception, emotion may be regarded almost as a 'feeling.' " In discussing more particularly our present theme he goes on to say: "Some sensations are neutral or devoid of effective tone, while others are rich in effective tone. The development of this latter is closely connected with the origin of the coaser emotions.

"That marked reactions of the nervous areas regulating the thoracic and abdominal organs (and the skin) contribute characteristically to the phenomena of emotion has been common knowledge from time immemorial. The fact of the connection is admitted on all hands, but as to the manner opinion is at issue. Does the psychical part of the emotion and its correlate nervous action then excite the viscera? or does the same stimulus which excites the mind excite concurrently, and, *per se*, the nervous centers ruling the viscera? or does

[4] Text-book of Insanity 1904 (Chaddock translation).
[5] The Integrative Action of the Nervous System.

the stimulus, which is the exciting cause of the emotion, act first on the nervous centers ruling the viscera and their action then generate visceral sensations; and do these latter, laden with affective quality, as we know they will be, induce the emotion of the mind? On the first of these three hypotheses the visceral reaction will be secondary to the psychical; on the second (hypothesis) the two will be collateral and concurrent; on the third the psychical process will be secondary to the visceral.

"The views of James, Lange, and Sergi have, common to them, this, that the psychical process of emotion is secondary to a discharge of nervous impulses into vascular and visceral organs of the body suddenly excited by certain peculiar stimuli, and that it depends on the reaction of these organs."

After describing some of his own extended work on this subject, and citing that of others on the same, he says: "Nevertheless, in view of these observations, the vasomotor theory of the production of emotion becomes, I think, untenable; also that visceral sensations or presentations are *necessary* to emotion becomes untenable. We are forced back toward the likelihood that the visceral expression of emotion is secondary to the cerebral action occurring with the psychical state." This latter statement I would interpret to mean that the visceral phenomena of emotion are due to cerebral reaction different in kind or grade from that which accounts for the psychical state of emotion.

While it may appear that here and elsewhere Sherrington successfully criticises the older conceptions, showing actual errors in the same from a physiological stand-point, it is not evident that he and others who have reached about the same deductions have greatly simplified the main question in our present discussion, namely, the relation of the peripheral nerve organs to the central nerve organs in the production of pain and paresthesia. We are certainly not yet in a position for a final disposition of the question. Therefore, we should not allow preconceptions of any kind to bias us in our efforts toward a practical clinical study of this syndrome.

I have for many years been attentive to cases which clinically fall within this category. Especially are the less severe and chronic ones more fascinating—cases which we are more tempted to carefully conduct and in which we are occasionally well rewarded for our care. We find a subject of this kind, or class, contending for months with a little chest paresthesia which probably vascillates in character or position, and is attended with more or less anxiety, often very little, the neurosis never at any time reaching a more serious phase. Again, we find another subject developing a skin or other paresthesia remote from the thorax in whom the sensory phenomenon finally shows enough spreading tendency and is accompanied by enough morbid anxiety to give us considerable concern. I have seen conditions of this description develop from attacks of acroparesthesia,

and I cited several interesting instances in a paper[6] some years ago. In some cases, as we know, the paresthesia reaches the intensity of pain, and when Krafft-Ebing, as quoted above, speaks of cases of precordial anxiety arising from neuralgias, he had, I believe, types of this kind in mind. Conditions of paresthesia are frequently met with presenting various clinical pictures. In dividuals of psychopathic predisposition, mental features often appear in the course of a paresthetic visitation, and they are invariably of the anxiety type, complicated at times, however, with other mental conditions. Cases presenting the anxiety complex sometimes, at a later period in their course, present the precordial phenomena, often only occurring at intervals far apart. *Vice versa*, others with a mild precordial tendency, later become the victims of a miserable anxiety psychosis.

In view of observation of this kind, Freud and others recognized a distinct type of neurosis to which he gave the name "anxiety neurosis." It would appear that there is good reason for the use of this separate descriptive name, which shall emphasize the distinction between this complex and conditions which are essentially neusathenic and hysterical, but which are often confused with it. We can only account for the phenomena which especially characterize the hysterical complex by the supposition of a distinct and fundamental type of reaction in some portion, at least, of the nervous mechanism involved. That this is equally true of the precordial complex there would seem little room for question. And if it is true, the practical importance of recognizing it is evident. For successful clinical study in psychiatry, as elsewhere, depends on a familiarity with all the possibilities in any situation under investigation. On this point I wrote some years ago as follows:[7]

"In attempting to analyze psychic symptoms we should never lose sight of the fact that with one essential or fundamental psychopathic tendency present and perhaps dominant in a case there are apt to appear at any time evidences of other tendencies which more or less obscure the picture. Hence it is always more important to learn all of a patient's particular temperamental and psychopathic tendencies than to become too soon anxious to fit him or his malady into a nosological system." This same injunction has been emphasized by others both before and since I expressed it as above. I am alluding to it simply to suggest that I am not unmindful of it at the present time.

As already stated, the excitation of peripheral organs as an etiological factor in the production of this complex is a fascinative side of the problem. The possible alterations in threshold which may here occur from various pathological processes is certainly very suggestive. The contemplation of such changes as probably result-

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[6] Acroparesthesia, Philadelphia Med. Jour., October 18, 1902.
[7] Imperative Pains, Jour. Nerv. and Ment. Dis., November, 1911.

ing from toxic agents has been a theme of more or less speculative
interest for many years. This interest will extend with increasing
knowledge, especially with more reliable information concerning
nutritional changes due to disturbances among the so-called internal
secretions.

In this whole study we are necessarily associated with co-workers,
with physiologists, internists, and surgeons, and with the internists
especially in the clinical handling of our patients. To our helpers
we must impart proper conceptions of the neurological problems
involved if we obtain from them profitable and convenient coöpera-
tion. This we can only accomplish when our own conceptions are
properly arranged and when we carefully plan our methods of con-
veying them to others.

We are all reminded daily of the inconvenience of lending these
neuropathic patients to the necessary observations of our most
friendly co-workers. This is more true of our anxiety subjects than
any other class, and is largely due to the fact that clinical workers
other than neurologists have not yet grasped the psychical char-
acters of the anxiety group and are not as cautious in dealing with
these patients as they are with the plain hysterical and neurasthenic
patients, with whose tendencies they have become somewhat more
familiar.

To impress this fact, in some part, for the common benefit of
ourselves and others was the thought foremost in my mind when I
ventured to write on this topic. We should remember that in deal-
ing with the anxiety patient we have a distinct neuropathic type
characterized by an overimpressionability, due in one instance more
to peripheral defect, in another to central defect, and often to defects
of both kinds. Hence it becomes very important to investigate all
possible peripheral complaints and signs in which these patients
abound, and yet not to let the patient's mind fasten on any particu-
lar locality while we are conducting our examinations. He should
be reminded cheerfully (not ominously) to await an intelligent
summation of the work of the various individuals constituting the
the diagnostic unit engaged on his case. This unit, according to
the better modern methods, is apt to include a number of individ-
uals, e. g., serologist, roentgenist, bacteriologist, internist, gynecol-
gist, surgeon, etc. That the lively imagination of the patient may
run the gamut of all these without serious contamination means
care on the part of the captain of the unit, in this instance the
neurologist. He must see that no important matter is really neg-
lected and still that his patient is not over worked *diagnostically.*

BRONCHIOLITIS OBLITERANS FOLLOWING THE INHALATION OF ACRID FUMES.

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The developmant of excessive quantities of fibrous tissue in the lung is a relatively frequent occurrence in adults. The majority of these fibroses, however, have no appreciable effect upon the function of this organ. At autopsy the presence of pleural thickening with subjacent pulmonary fibrosis receives but passing notice, and the sclerosis of the lymphatics, particularly as a consequence to moderate grades of anthracosis, are noted during the examinaton of the tissue. The development of connective tissue under these circumstances does not encroach to any extent upon the alveolar structures, and the compensatory activity of the remaining lung is sufficient to carry the new burden without evincing any clinical symptoms. Under these conditions the bronchioles are in no way affected. Fibroses are also common in the areas of healed tuberculosis. These are most frequently encountered in the apex of the lung when more or less puckering is produced. But here, again, the larger tracts of lung tissue remain uninvolved and the effect upon the respiratory function is usually negligible.

More important are the fibroses which diffusely or sporadically involve the parenchyma of the lung. In interstitial pneumonia somewhat large areas of the lung tissue show a thickening of the alveolar walls, often developing to such an extent that the air sacs are considerably narrowed. Under these conditions the fibrosis localizes about the vascular channels in the alveolar septa, and to some extent about the bronchioles. The latter may eventually suffer narrowing of their lumina through the contraction of the surrounding fibrous tissue. Portions of the lobes or even an entire lobe may be thus sclerosed and have but little value for respiration. The remaining portion of the lung tissues may adequately compensate the lack of function in this portion of the lung and the individual show no signs of the respiratory impediment.

Finally, there is another type of fibrosis which, although less frequent, has a clinical importance. This type has been referred to as fibrous pneumonia. The condition is met with in various forms, sometimes appearing as a lobar process representing an unresolved organizing lobar pneumonia, at other times being found as a lobular process. It is particularly the latter group in which our interest at the present time is centered. This lobular pulmonary fibrosis shows the presence of connective-tissue plugs filling the air sacs

in small clusters of alveoli. Outside the affected portion of the tissue the alveoli are relatively normal. Thus one finds scattered through the lung substance small areas of fibrosis which tend to obliterate groups of air sacs and appear as milia widely disseminated. Here, again, an analysis distinguishes types of this fibrous broncho-pneumonia. Some of them, and they are the majority, arise as a sequel to an acute bronchopneumonia and simulates the fibrosing process observed in the organizing unresolved pneumonia. A smaller group, however, and of these there are only 6 cases on record, the condition appears to arise primarily within the bronchioles and a few neighboring alveoli. In them there is no evidence of a pre-ceding acute bronchopneumonia with organization of its exudate, but the fibrosing process appears to arise spontaneously from the walls of the bronchi and alveoli. In some instances an irritant has been briefly present inducing an inflammatory reaction, but in others no such irritant can be demonstrated. The irritant has usually been of the nature of irritating gases to which the individual has been accidently subjected. The following case is one of this latter group:

CASE HISTORY. J. C., male, aged thirty-nine years, a laborer in a chemical works, gave a history of good health until the present illness. He also gave a history of lues with secondary skin lesions (time not stated) as well as a gonorrheal infection three years ago. He has used tobacco considerably.

Present Illness. The patient dates his present illness to an explo-sion at the chemical works three weeks previous to admission to the hospital. In this explosion, when various chemicals were being mixed in the preparation of trinitrotoluene, he was subjected to the breathing of irritating gases. Other than the discomfort and cough at the time of the accident he was not seriously ill. A few days later, however, he suddenly became dyspneic, at first observed on slight exertion, but later being continuous and accompanied by much sputum. The symptoms became progressively worse, along with a feeling of drowsiness and the development of edema of the ankles.

Physical Examination. He was a slightly built man, assuming the upright posture in bed. He had great respiratory distress, a dry, hacking cough, marked cyanosis, and a general slight anasarca. His pupils were irregular and reacted poorly to light and accommo-dation. His oral hygiene was poor, the tongue being coated, and the teeth showing pyorrhea alveolaris. Marked carotid pulsations were observed in the neck.

The heart occupied a normal position and showed no change in size. A blowing murmur transmitted to the left axillary region was heard at the apex. There was a slight diastolic murmur at the apex, also heard at the second right interspace and transmitted along the vessels of the neck.

The respirations were short and snappy. Tactile fremitus was

increased over the left upper lobe anteriorly; over this area the percussion note was somewhat flat. Auscultation revealed moist crepitations over the greater portion of both lungs. Tubular breathing was present over the left upper lobe.

There was slight movable dulness in the flanks of the abdomen and the extremities showed edema about the ankles and hands. There was a small amount of albumin in the urine, with an occasional hyaline and granular cast. The temperature reached its highest at 101.8° F. The red blood cells numbered 8,710,000, the white cells 28,000, and hemoglobin 94 per cent.

During his stay in the hospital (three days) two phlebotomies were done, removing 275 and 300 c.c. of blood respectively. This procedure relieved the dyspnea and lowered the blood-pressure from 190 to 165. The patient felt much better each time. While in the hospital the marked symptoms presenting themselves were dyspnea, cyanosis, and some edema of hands and feet. Fourteen hours after the last phlebotomy the patient became very dyspneic, with a weak running pulse. The patient died unexpectedly, gasping for breath. An autopsy was performed six hours after death by Dr. W. W. G. Maclachlan.

Autopsy Report. The body was that of a well developed, well-nourished adult male. There was much edema of the subcutaneous tissues, particularly at the ankles. The chest was well formed. There was a white scar on the prepuce, 1.5 cm. in length, at the right upper border of the corona.

Neck Organs. Near the bifurcation of the trachea there was some congestion of the mucosa, with a little frothy mucus in the lumen. The glands at the bifurcation were large, soft, anthracotic, with dull areas of congestion. These did not show evidence of tuberculosis.

Thorax. There were fibrous adhesions on both sides over the posterior lobes of the lungs and about 200 c.c. of clear amber-colored fluid was present in both pleural sacs.

Left Lung. The lung was much heavier than normal, weighing about 700 grams. The posterior surface of the lower lobe showed many fibrous tags of adhesions. The upper lobe was adherent to the lower by similar adhesions, but the posterior surface was smooth. The lung felt firm, particularly in the lower lobe, but considerable crepitation was still evident in it. The cut surface of the lung showed in the lower lobe a moist, glassy surface which, on pressure, exuded a frothy brownish-red fluid. The surface of the lower lobe had a dull, pinkish-gray color, with here and there ill-defined areas of varying sizes, which were even darker red, and which, although glassy when scraped with the knife, appeared a little granular. Several minute pieces of the lung from these areas sank in water. Further, there were scattered through the lower lobe small, irregular round masses of white fibrous tissue. The

small, round forms looked like tubercles, but were not typical, while the larger, irregularly shaped areas had a true fibrous appearance. The fibrous areas were abundant and gave the lung a marked increase in consistence, and further produced a somewhat mottled red and white color to the substance where these nodules were numerous. In places the distribution of the fibrosed areas had a bronchial arrangement, and, further, it seemed evident that some of the round masses were connected with the small bronchioles. The cut surface of the upper lobe showed about the same general appearance as the lower, only there was neither as much congestion nor edema, nor were the small fibroses as numerous, but they were still very evident. The bronchi of the lung showed much congestion of the lining and considerable frothy mucus. The peribronchial lymph nodes were anthracotic, but showed no tuberculosis.

Right Lung. The lung was enlarged and showed numerous fibrous tags over its posterior surface. The organ was generally firm, but crepitation could be elicited in most places. On section through the lung there was a general similarity of all the lobes. The amount of congestion and edema was much more evident in this lung. On squeezing it a brownish, frothy fluid escaped in large quantities. The upper lobe contained almost as much as the lower. The cut surface had a very glassy, slightly reddish color, with here and there some darker portions in the lower lobe, suggestive of hypostatic consolidation. Scattered through the lower lobe were numerous small areas of fibrosis similar to those in the left lung. Some of these were small and round, about 2 mm. in diameter, apparently having some relation to the bronchioles. Others were more irregular in their size and shape, although they never were large. The lower lobe was of much increased consistence. The upper lobe did not present so many areas of fibrosis, while in the middle lobe they were but rarely seen. The bronchi showed much congestion of the lining and a great deal of frothy mucus in the lumen. . The peribronchial glands were large, anthracotic, rather soft, but showed no tuberculosis.

The heart showed no evidence of any valvular lesion, but the myocardium of the left side showed some hypertrophy. The aorta had occasional nodules of endarteritis and considerable wrinkling and puckering of the inner surface of the arch. The abdominal cavity was free from fluid. The liver, pancreas, and spleen showed nothing unusual, save some congestion. The kidney was pale, the cortex granular. The glomeruli were somewhat congested. The cortex was increased in width.

Microscopic. Lungs. Sections were made from various portions of the lung. By the naked eye one could discern small, solid masses occurring within the spongy tissue. These areas were at times directly beneath the pleura as well as in the

deeper parts of the lung tissue. These tissue masses were found to be associated with the bronchioles. In these areas the normal structure of the lung was almost obliterated by a tissue reaction of an inflammatory nature. It was found that the stage of the inflammation was not the same in all parts, but in some a progressive reaction with an acute exudate was the prominent feature, while in others, stages of advanced granulation tissue were found.

The lung tissue between these foci of inflammatory reaction was of fairly normal character save for the presence of some congestion, a little edema, and occasional red cells within the air sacs. At times a dilatation of the alveoli suggested a compensatory emphysema; this, however, was never marked.

The punctate areas of inflammatory response were directly associated with the presence of a bronchiole lying more or less centrally within the areas of sclerosis. The inflammatory reaction always included the bronchioles with its surrounding connective tissue and a few of the neighboring alveoli. Thus there was an involved area resembling the nodules of inflammation in bronchopneumonia. In this case, however, the areas were much smaller, there being only a few alveoli surrounding the bronchioles which were attacked.

In places the bronchi and bronchioles were filled with red blood-cells, desquamated epithelium, and many polymorphonuclear leukocytes, lymphocytes, and plasma cells and fibrin. This sub-acute inflammation when present infiltrated the walls of the tube (bronchiole) and extended into the surrounding alveoli. In those areas where the desquamation of the lining epithelium was more marked there was a definite fibrinous exudate. This exudate showed evidence of organization by the proliferation and ingrowth of the connective-tissue cells of the wall. The muscle fibers were separated by the invasion of fibrous tissue from the surrounding stroma, which advanced by many prolongations into the lumen. In these areas of organization many new-formed and congested blood-vessels were seen. In other areas the bronchi and bronchioles contained a granular exudate in which there were occasional desquamated cells. Their walls had an irregular outline and appeared to be shrunken, and in one or two instances, more or less collapsed, obliterating almost half of the lumen. In these cases, where the walls approximated each other, many small strands of fibrous tissue were soon extending from wall to wall in a process of complete obliteration. Occasionally only half of the bronchial wall could be identified, with a dense mass of connective tissue lying along its side. The muscle tissue of the remaining portion of the wall could be readily recognized, while only an occasional strand was found in the adjoining connective tissue.

In places many bronchioles were filled with polymorphonuclear cells, fibrin, and granular debris. Along one border the lining epithelial cells were often missing while on the opposite side they were

present in an irregular manner, beneath which there was a marked proliferation of the subepithelial connective tissue continuous with the fibrous tissue of the outer portion of the bronchial wall. The most prominent areas of fibrous induration were in the peribronchial portions. Here the true increase of the fibrous tissue was seen. At times it was cellular or again more dense in character, and of an adult appearance. The denser connective-tissue cells had immature characters. From this peribronchial connective tissue many extensions were seen in the septa of the neighboring alveoli giving them a thickened appearance, and at the same time diminishing the size of the alveolar cavity.

The alveoli also showed a variety of changes. They were, as a general rule, fairly normal looking, but uniformly small. In the immediate neighborhood of the bronchi and bronchioles the walls of the alveoli were definitely thickened by fibrous connective tissue. In the distal areas the alveoli contained a large number of red-blood cells and relatively few desquamated epithelial cells. Again, in other areas the alveoli were filled with cells of true inflammation of the polymorphonuclear, lymphocytic, and plasma-cell varieties. In these instances various stages of organization by newly formed fibrous connective tissue were observed. Various stages, from the early formation of fibroblasts and new bloodvessels to complete organization and obliteration of the alveoli by a dense fibrous connective tissue plug, were found.

In the intermediate alveoli or those situated more distantly from the bronchi and bronchioles a more normal appearance was maintained. However, there were relatively few in which no change had taken place, as they commonly contained red blood cells, desquamated epithelium, or had a slight fibrous increase in their wall. In places the epithelial lining of the alveoli and bronchioles was lifted from its basement membrane by a proliferation of fibroblasts extending toward the lumen. This fibrous tissue was continuous with the newly formed peribronchial fibroses. In the thick bands of fibrous tissue which course through the lung, as described above, many alveoli were found occupied or replaced by the growth of the firm fibrous tissue network. The infiltration of cells was not limited to the lumina of the bronchi and alveoli, but was also observed in the walls of these structures.

The bloodvessels and lymph vessels were considerably thickened. This thickening was due to a marked increase in the outer coats of the bloodvessels or their adventitial connective tissue. The sclerosis was quite loose and composed mostly of collagen fibrils and relatively few elastic tissue fibers. In the larger bloodvessels there was a slight increase in connective tissue of the intima.

Aorta. Sections of the aortic arch showed much change of the vessel. The intima was greatly and irregularly thickened by a laminated hyaline connective tissue. At the junction between the

intima and the media there were a number of cellular collections of inflammation around small bloodvessels. Some of these vessels entered the deeper portions of the intima. The media was much affected by focal inflammation and degeneration. These focal areas were found in all portions of the media and consisted in central vessels surrounded by lymphocytes and plasma cells. About these areas the tissues showed degeneration. In places the musculature and elastic tissue were completely interrupted. By elastic-tissue stain one could distinguish various grades of degeneration, with complete destruction of elastic fibers. The adventitia was much thickened by fibrous tissue in which elastic fibers were almost wanting. The vasa vasorum showed thickening of their walls, particularly of the intima, with narrowing of their lumina. Occasionally, lymphocytic and plasma-cell infiltrations were observed around the vessels of the adventitia.

Liver. The liver lobules were fairly well preserved and the columns were quite regular. There was some lymphocytic infiltration about the portal system, with a slight increase in connective-tissue cells. A greater number of leukocytes were seen scattered throughout the liver than are normally seen in the sinuses. Two small areas of focal necrosis with lymphocytic infiltration were observed. In some instances the sinuses were rather deeply congested, but this was not uniformly present.

Kidney. Sections of the kidney showed the cortical tubules enlarged. These tubules were lined by an irregular, low epithelium which had large poorly staining nuclei and finely granular or nebular cytoplasm. The lumina of these tubules contained granular débris. The glomeruli were all enlarged and surrounded by a thin capsule. They showed no evidence of acute inflammation, but had in some instances a rather degenerated appearance. In a few instances a few polymorphonuclear leukocytes were seen in the glomeruli. The capillaries in the glomeruli were patent and in some instances concongested. Elsewhere, again, there was evidence of bands of inflammatory reaction running through the cortex and involving the glomeruli and tubules. Within these areas there was an excess amount of connective tissue. This was infiltrated with lymphocytes, polymorphonuclear leukocytes, and plasma cells. The involved glomeruli showed a thickening of the capsule with hyaline change. Synechiæ were common, and where found the glomeruli were involved in the same change observed in the capsule. The hyaline change gradually progressed in the capsule until a whole glomerulus was obliterated.

Sections of the heart, pancreas, spleen, and prostate showed no definite pathological change.

To briefly review the foregoing case the following are the main facts: A man, aged thirty-nine years, with an antecedent history of lues, was accidentally subjected to the inhalation of irritating

gases.   At the time of the accident he suffered nothing more than
a sever fit of coughing.   Three days later dyspnea suddenly de-
veloped, increasing continuously until the time of his death, three
weeks later.   During his illness his most marked clinical manifesta-
tions were dyspnea, cyanosis, and some edema of the feet and hands.
Clinically, no pulmonary consolidation could be discovered, but the
chest examination indicated mainly a bronchial involvement.   At
autopsy numerous small fibrous foci were observed in the lung
tissue, suggesting miliary tuberculosis, but not showing any evidence
of necrosis which marks these lesions.   The microscopic analysis
showed the presence of inflammatory reactions in and about the
bronchioles, accompanied by a process of organization.   In this way
it differed from a process of bronchopneumonia, to which, however,
it had the closest resemblance.   The lesions had no relation to
tuberculous infection.   Their remarkable feature lay in the process
of resolution.   The early acute inflammatory processes resembled
an exudative bronchiolitis in which leukocytes, fibrin, and epithe-
lial, lymphoid, and plasma cells constituted the main bulk of the
exudate.   The inflammatory reaction, however, was not alone con-
fined to the development of an exudate lying within the ramifica-
tions of the bronchi, but there was a tendency to bring about tissue
change in the neighboring structures.   The bronchi showed more or
less desquamation of their epithelial lining and their walls and sur-
rounding connective tissue were stimulated to proliferate.   In all
areas there was evidence of connective-tissue growth whereby the
outer portion of the bronchial wall became thickened, while a granu-
lation tissue formed bulbous ingrowths into the lumina.   Thus
bronchi were found which were narrowed partly by the shrinkage
of the peribronchial fibrosis as well as by organic plugs filling the
lumen.   Associated with these organizing inflammatory reactions,
more or less of the surrounding air sacs were involved in a similar
process.   Numerically the number of air sacs involved were rela-
tively few, as there were wide stretches of lung tissue in which the
inflammatory process had no effect.   The presence of red-blood
cells in the outlying alveoli was a terminal condition associated with
the intense dyspnea accompanying the fatal outcome.   The in-
volved alveoli were disturbed by a fibrosing process very similar to
that of the bronchioles.   A thickening by fibrous tissue involved
the alveolar septa while an ingrowth of granulation tissue occluded
to a greater or lesser degree the air sacs.   To some extent the sclero-
sis involving the bronchi and neighboring air sacs also encroached
upon the lymphatic channels and bloodvessels in the surrounding
trabeculæ.

A number of cases of bronchiolitis obliterans have been reported
in the literature.   Clinically and pathologically they have a close
similarity.   In all of them dyspnea and cyanosis is the most important
feature, and in many this is of sudden onset.   Etiologically, however,

the reported cases may be divided into three groups: In the first group are the cases of apparently spontaneous origin in which no antecedent history indicates the reason for the organizing inflammation. Such cases were reported by Lange (Case I), Karwicka and an unreported case by Cobet, of Marburg. These cases bear a striking similarity in their sudden onset and absence of preceding illness. Dyspnea is usually the first indication of illness, and rapidly progresses with fatal termination in forty-eight to seventy-two hours. No definite etiology has, as yet, been determined for this group. Group two includes the cases in which a definite history of preceding bronchopneumonia has gradually led to an organizing pneumonia of the lobular type. Cases of this kind following measles, chronic bronchitis, and foreign bodies in the bronchus have been reported by Lange, Vogel, Müller, Wegelin, Hart, Ribbert, Pernice and others. In this group the process of organization is not unlike that observed in the organizing pneumonia of the lobar type. A considerable study and discussion have been made upon the factors leading to the development of granulation tissue in the various forms of infectious pneumonia. Just what conditions modify the responses in the lung which, under certain conditions, lead to complete resolution, while others bring forth granulation tissue, is still far from clear. The third group, of which the case here reported in one, consists of cases in which individuals have been subjected to the inhalation of irritating gases. Fraenkel, in 1902, studied a case of bronchiolitis obliterans in a man, aged twenty-five years. During his work as a brass-moulder he was accidentally subjected to the fumes of nitric acid. Dyspnea and cyanosis became marked on the third day, and he died at the end of three weeks. Edens reported a similar case of inhalation of hydrochloric acid and sulphuric acid. Here, again, after the initial sense of choking, dyspnea became a marked feature on the second day. Gradually the dyspnea improved and the patient was well at the end of a month. Edens reported a third case in which the patient suffered from the inhalation of ammonia. To this third group we must add our own, which is very like that reported by Fraenkel.

It is probable that a pathological distinction cannot be made between the lesions found in the three groups. The fibrosing process has in all of them a close relation to an inflammation in the bronchial walls. There is some variation in the character of the exudate in the different cases, but the process of repair appears to be common in all. Wassiljew makes a distinction between the organization of an exudate of a preceding acute inflammation and the development of a granulation tissue arising from the bronchial wall or septa of the alveoli. Such a classification cannot, however, be applied to all of these cases, as some are found with evidence illustrating each mode of fibrous-tissue production. In our own case the growth of bulbous masses of granulation tissue

was more prominent than the ingrowth of fibroblasts through the meshes of an antecedent fibrinous exudate.

The reports upon fibrosing bronchitis have mainly dealt with a study of the origin of the connective tissues. Some attempt has been made to explain the reason for the abnormal growth of fibrous tissue as compared with the usual outcome of inflammatory processes in the parenchyma of the lung. Up to the present these explanations have not been entirely satisfactory. Undue stress has been placed upon the differences between the growth of the connective tissues during the organization of an inflammatory exudate and its apparent spontaneous proliferation from connective tissue containing areas. These points of differentiation were a prominent part of the discussion at a time when it was believed that the inflammatory cells of an exudate gave rise to the fibroblasts of organization. When, however, at the present time it is accepted that the fibroblasts appearing during the stage of repair of an inflammatory process have their origin from fixed connective-tissue cells of the injured area, the polemic upon the differences of connective-tissue growth with or without the presence of fibrinous exudate no longer has such an important meaning. Karwicka, Edens, Lange and others have all shown that the fibrous tissue found in obliterating bronchitis has its origin from a similar tissue in the walls of the bronchioles. At times it appears to arise from the submucosal tissues, while in other instances, and particularly when the reaction is more extensive and the peribronchial stroma is in active proliferation, the intratubular masses appear to originate from these outlying structures. The observation has been repeatedly made that the proliferating peribronchial tissues break through the muscular ring and present themselves in a warty growth inside of the bronchi. That this ingrowth actually occurs may be seen in the presence of anthracotic pigment carried inward with the stroma from the peribronchial deposit. A similar overgrowth of the connective tissue also appears within the air sacs. Here, however, one also finds evidences of organization of exudate as is commonly observed in areas of aseptic repair.

Another point in regard to the inflammatory process of the bronchial wall is the sequence of events as may be observed in those cases. True it is that observations have not been made upon the lung reactions from the time of injury until death; nevertheless, in these peculiar cases various grades of the reaction may be observed in the same specimen. It is probable, as indicated by the clinical manifestations, that congestion and edema are among the early effects upon the bronchi and their branches by the inhalation of irritant. gases. A serous flow from the mucosal surfaces leads to the expectoration of considerable quantities of thin sputum. Following this a desquamation of the epithelial covering denudes much of the bronchial wall. In one case reported by Edens the exfolia-

tion of the mucosa permitted the patient to expectorate partial casts of the bronchial tubes. Such an extensive desquamation is unusual. Microscopically, however, all of the cases showed fairly large areas from which the mucosa had been removed. At these points the bronchial wall becomes subject to a more deeply infiltrating inflammatory process than those areas in which the mucosa remains intact. Moreover, it is at these denuded sites where the proliferative reaction of the connective tissue is prone to occur. It is probable that the unequal distribution of the injury upon the bronchial wall is in part dependent upon the presence or absence of layers of mucous secretion. The finding of greater damage in the bronchioles as compared with the lung tissue probably results through spasm of the distal portions whereby the gas is not admitted into the alveolar structures. This is similar to the spasm of the esophagus observed in children upon accidentally drinking strong caustics. In the latter instance the caustic fluid does not reach the stomach, but is momentarily held through spasm of the cardia in the lower portion of the esophagus. The alveoli of the lung, which show a process of organizing inflammation, appear to be involved because of their proximity to the damaged bronchioles.

Thus the bronchioles directly influenced by the acrid gases suffer desquamation of their epithelium and have their deeper tissue injured by the primary noxious agent. The reaction in these tissues is of stimulating kind, whereby a varying amount of migratory exudate permeates their interstices and also whereby the irritant acts as a stimulating factor upon the connective tissues. Whether a further stimulus is induced through the presence of bacteria and their toxins or by the effect of products of decomposition is difficult to say. It appears, however, evident that the primary irritant has in itself a peculiar effect in leading to tissue overgrowth.

It is evident that the fibroses appearing under the conditions as we have described differ materially from those arising in the lung through other agents. The fibroses associated with tuberculosis, actinomycosis, and aspergillosis of the lung appear in localized areas of tissue destruction in an attempt to repair limited damage. The stimulation for the growth of connective tissue under these conditions is not greater than the demand necessary for such repair. Similarly, the fibroses occurring in and about the lymphatics of the lung as the result of the presence of foreign materials (coal dust) is limited in its extent and relative to the irritating effect of the foreign material. Infiltrating fibroses are sometimes seen in the periphery of the lung advancing from areas of chronic pleurisy, but these again are usually localized and in proportion to the extent and chronicity of the infectious and inflammatory products. More closely allied to the proliferation observed in obliterating bronchitis is the organization of unresolved pneumonia. Some comparable features are here observed. Under these conditions the alveoli

filled with exudate show more or less desquamation of their lining epithelium. An irritant differing from that usually present in lobar pneumonia stimulates an interstitial reaction in which the connective-tissue cells are also involved. If their response is one of proliferation the alveolar sac is invaded and it may be occluded. The presence of exudate assists in directing the growth of the fibroblasts and in producing synechiæ. It has been a not uncommon observation that cases of indurative pneumonia also show some bronchial involvement. A series of these cases was studied by Wassiljew, who believed that the bronchial lesion was independent of the changes in the alveoli, though probably the result of a common cause. He found the intratubular fibrous tissue of the nature of a true granulation tissue. An interesting experiment was undertaken by him in which a bronchopneumonia was induced in dogs and rabbits by injecting a 2 per cent. solution of agar into the bronchi. By this means he was able to induce a fibrosing process partially occluding these tubes. These experiments, however, simulate more closely the induction of fibrous-tissue proliferation in the vicinity of foreign bodies.

The intense clinical manifestations of dyspnea are referable to the stenosing process in the bronchioles. Not alone do the bronchioles suffer obstruction through the presence of fibrous plugs, but the narrowed tubes tend to accumulate masses of mucus at the points of constriction. Moreover, it is probable that the spasmodic attacks of dyspnea result from an increased irritability and convulsive muscular contractions of the bronchioles.

It would be interesting to know whether the late effect of the gas-poisoning upon the European battle-fields is of the nature of a fibrosing obliterative bronchiolitis.

I wish to express my sincere thanks to Dr. Oskar Klotz for his assistance in the preparation of this paper.

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SYPHILIS OF THE NERVOUS SYSTEM IN SOME OF ITS CLINICAL AND PATHOLOGICAL MANIFESTATIONS.[1]

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It is my[2] opinion that in tabetic ocular palsies, as well as in those recognized as syphilitic ocular palsies, the lesion is not primarily nuclear but is in the nerve fibers as they leave the brain, and I have reported a case of tabes with intense ocular palsies in which the microscopic findings gave much lymphocytic infiltration of the ocular nerves. I am not prepared to state a conviction that primary nuclear palsy of the cranial nerves in tabes is impossible, but I do believe that most tabetic cranial nerve palsies are primarily radicular, and that when nuclear changes are found in tabes they occur in cases of long standing. It is to be expected that when nerves have been degenerated near their nuclear origin during a period of years the nerve cells from which these degenerated fibers arise should show alteration. This view-point is of therapeutic as well as pathological importance, for if the degeneration be in the nerve we may expect recovery from persistent antisyphilitic treatment, provided the degeneration be not too intense and the treatment be begun early; whereas we may expect much less improvement if the cells of origin be primarily affected.

There are cases in which syphilitic ocular palsy is not caused by basal meningitis but by softening implicating the nuclei or nerve fibers of the affected nerve, and a case of bilateral softening forming two separate foci in the oculomotor nuclei I[3] described in 1913.

It is well known that tabetic palsies often disappear, and this subject was discussed by Posey[4] in a symposium on the "Neuroocular Symptoms of Tabes" in April, 1915. He stated that it is an almost constant experience that the palsies that appear in the early stages of the disease vanish after periods of persistency ranging from but a few hours to two or three weeks; and while it is true that the palsies that occur in the later stages are, as a rule, permanent, even these may be transient and may totally disappear, usually after a longer period than when they are observed at the commencement of the disease.

Posey found that the palsies vanished for a time, at least in perhaps 90 per cent. of the cases which he had under observation.

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[1] Read as part of a symposium on syphilis held at a meeting of the College of Physicians of Philadelphia, February 7, 1917.

[2] Spiller: Jour. Nerv. and Ment. Dis., January, 1915, p. 15.

[3] Spiller: Le Névraxe, 1913, xiv.

[4] Pennsylvania Med. Jour., October, 1915, p. 55; Jour. Am. Med. Assn., April 16, 1910.

This percentage was based on an analysis of the history of 60 cases taken from his own records and from the study of 28 cases of advanced tabes which he had at one time made in the wards of the Philadelphia General Hospital.

The tendency of the palsies to recur was also dwelt upon, either the same muscles being repeatedly palsied or the paralysis appearing in one or more muscles shortly after it had disappeared in a muscle governed by the same nerve. In some cases the palsy may pass away in a few hours; in others it may persist for years. This return of the muscle to its normal even after years of paralysis he thought should be recognized by ophthalmic surgeons, and should tend to discontinue operations on the eye muscles of tabetics. Tabetic palsies are usually dissociated. This is essentially true when the palsy appears as an initial symptom.

It is important to determine how long an ocular palsy in cerebral syphilis may persist and yet have a final recovery. An interesting case from this point of view is the following: Oscar T., aged thirty-two years, was referred from Dr. de Schweinitz's service April 11, 1914, to the neurological department of the University of Pennsylvania with the note: "Complete palsy of the left external rectus muscle; pupils 3 mm.; no fundus changes; light reaction of pupils gone; faint convergence reaction."

The man contracted syphilis at the age of twenty years.

The symptoms began three weeks before he came to the hospital, with dizziness, and this was soon followed by rapidly developing diplopia. He had headache of moderate intensity, tinnitus in the right ear, paresthesia in the lower limbs, and a sense of constriction about the knees. Station and gait were normal. The patellar reflexes were normal, but the Achilles reflexes were lost. He had no disturbance of the bladder and no disturbance of sensation, even in the distribution of the lower sacral roots. Slight outward rotation of the left eyeball was observed May 6, 1914.

The next note made was on December 24, 1914: "Ocular palsy seems less than it was eight months ago." He was taken into the hospital on this date. He had diminution of pain sensation in the first and second divisions of the right fifth nerve. On December 29 Dr. Langdon reported: "Central vision normal in each eye and fields of vision normal for form and color, although disks show some pallor in temporal portion. No other fundus changes. O. D. pupil 4 mm. O. S. 3.5 mm. Both Argyll Robertson."

Dr. Butler found the hearing apparently normal.

The Wassermann reaction was negative. He was given the protiodide of mercury, gr. $\frac{1}{3}$.

February 14 and 15 the note was made that the motion in the left eye was gradually returning. February 24 the external rectus palsy had almost disappeared. March 4, Dr. de Schweinitz found concomitant squint was about 15 degrees; the left external rectus

now moved the eye to the outward commissure by 33-degree prism base out.

Slight improvement began soon after the patient first came under observation, but the restoration had not amounted to much ten months after the onset of the palsy, although the man had been treated for syphilis at another hospital. Then the improvement advanced rapidly. At the present time there is only slight ocular palsy.

Another case of long-standing ocular palsy with final recovery occurred under the observation of Dr. de Schweinitz, as shown in a letter from him March 5, 1915: "Referring to our conversation in regard to the recovery of long-standing palsies of the exterior ocular muscles, I have to say that the patient concerning whom I spoke to you is a woman, aged fifty-eight years, whose eyes I have known since the middle of November, 1892, correcting them at stated intervals for a varying hyperopic astigmatism. February 24, 1914, she came with a history of three weeks of diplopia and much left-sided neuralgic pain. She was excessively nervous; there were no nasopharyngeal troubles; no history of rheumatism. Urine examination was negative, but both the Wassermann and the Noguchi reactions were positive, the examination having been made by Dr. Corson White. The left external rectus was the muscle involved, and no other exterior ocular muscle was affected. The palsy was not quite complete, and the diplopia neutralized by a 25- to 30-degree prism base out. I knew that she had been under the care of a man who has a sanitarium, and asked him for some data. He tells me under date of April 18, 1914, that five years previously she had been under his care in his sanitarium because 'her family feared insanity.' He then goes on to say: 'I found no signs of mental unsoundness, and the patient recovered rapidly in about a month's time. I ascribed her condition at that time to the nervous phenomena which follow the menopause.' This paresis of the left abducens remained practically stationary; in point of fact, for the first few days it increased so that there was practically no movement outward. I say 'practically' there was, perhaps, 1 mm. of movement on strong efforts at abduction, and the diplopia could be with difficulty neutralized with very high prisms between 40 and 50 degrees. At first a mixture of iodide of sodium and aspirin was tried. This was soon stopped and iodide of potassium and bichloride of mercury were ordered. There was practically no improvement until about the middle of August of the same year—that is, six months after treatment was begun—when the diplopia became less marked, the neutralization first requiring between 25 and 30 degrees of prism and then between 15 and 20 degrees, and the movement of the eye was slightly improved, the first record of increased movement being on August 12, 1914. During all this period of time, with the exception of the first week, she took very large doses of iodide

of potassium, never less than 90 grains a day, and sometimes as
much as 100 grains a day. Between August 12 and December 9
the diplopia remained practically stationary, neutralized by a 15-
to 18-degree prism. Indeed, this condition of affairs did not alter
materially, maybe only 2 or 3 degrees, until January 7 of this year,
when the diplopia had dropped to 7 degrees, and at the last examina-
tion, on April 10, was not noticeable, although it could be developed
by a red glass, and the movement of the eye was practically normal."

The cause of such palsy, as already said, is usually basal syphilitic
meningitis, as illustrated in the following case, which is like the one
described by me in 1915:

J. H., aged fifty years, entered the service of Dr. Solis Cohen
November 17, 1914, having pneumonia, and died November 29,
1914. He was delirious and consequently a thorough examination
could not be made. He had ptosis of the right upper eyelid, the
pupils were unequal, and the right was larger and did not react to
light. There was obliteration of the lines of expression. In May,
1914 the note was made that he had partial ptosis of the right upper
eyelid, the right pupil was larger than the left and irregular, and did
not react to light or in accommodation. The right eyeball was
rotated outward. He had almost a complete right oculomotor
palsy, as he had very slight movement of the right eyeball inward,
upward or downward. The left iris did not react to light but did in
convergence. The movements of the left eyeball were normal. The
oculomotor palsy had developed rapidly a year and a half pre-
viously. He was able to count fingers readily with either eye, and
examination of the eye-grounds revealed nothing abnormal. He was
brought to the hospital because of the ocular condition. He did
not comprehend questions readily, was somewhat confused as to
time and place, and his memory was feeble. The patellar reflexes
were absent.

The microscopic examination in serial sections of the cerebral
peduncles showed moderate infiltration of mononuclear cells in the
pia at the exit of the oculomotor nerves and disappearance of many
nerve cells in the oculomotor nuclei. The origin of the ocular palsy
was probably the syphilitic basal meningitis. The posterior columns
in the lower part of the medulla oblongata were degenerated as in
tabes, and the case was evidently one of tabes, although the spinal
cord was not obtained.

Stargardt[5] investigated the causes of optic atrophy in tabes and
paresis in 25 cases, and examined the visual system from the external
geniculate body to the retina. When the optic nerve was normal
the retina also was normal. Where changes occurred in the retina
they were secondary to changes in the optic nerve and differed in
no way from those observed after division of the optic nerve or

[5] Allg. Ztschr. f. Psychiat., 1912, lxix, 735.

compression of this nerve by a sclerotic internal carotid artery. The cause of the optic atrophy was exudative processes in the chiasm and the intracranial portion of the optic nerves. The optic tract and external geniculate body showed only secondary degeneration. In cases of partial optic atrophy the atrophy was the result of partial infiltration of the intracranial portion of the optic nerve. He concludes that there was no ascending atrophy from any intoxication of the ganglion cells of the retina, as has been assumed. In all cases of optic atrophy he found infiltrative processes in the parts about the chiasm and the optic nerves. The changes in the optic nerves therefore resemble those in the nerves supplying ocular muscles.

It has been my custom for years in studying syphilis of the brain in the laboratory to examine especially the cerebral peduncles and optic chiasm, because if there are manifestations of syphilis in the brain it is here especially we may expect to find lesions. It is because this region of the brain is specially liable to be affected by syphilitic lesions that syphilis may cause the symptoms of tumor of the pituitary body.

I have seen several cases of complete bilateral isolated paralysis of the seventh nerve in syphilis with recovery, and two such cases observed in my service are reported in a paper by Harvey W. Ewing.[6] The lesion must be an infiltration of mononuclear cells in the pia, but it is indeed strange that two nerves of similar distribution, but remote from one another in origin, should alone be picked out by the syphilitic lesion. I have also seen implication of the fifth nerve alone, and reported such a case with necropsy with Camp.

It is desirable to remember that permanent results were accomplished in the treatment of nervous syphilis in some cases before the days of salvarsan and the modern laboratory methods of investigation. Unfortunately, we must confess that our modern methods, while usually of great value, are not satisfactory in all cases of nervous syphilis, and that some cases do not respond to any treatment, and others may respond and then relapse. I have had the opportunity recently to reëxamine a man who, in 1897, was in the service of Dr. James Hendrie Lloyd[7] at the Philadelphia General Hospital, and whose case was reported by Dr. Lloyd at that time.

The man then was twenty-one years of age, and had a history of syphilis. His symptoms of syphilitic disease of the nervous system were pronounced, and he improved greatly under the administration of mercury, and possibly iodide, and has remained in this improved condition during nineteen years. At present this man is in very fair condition; he has gained flesh, and aside from his polyuria and third nerve palsy, which he has had since 1897, he has few signs of disease. He is employed as a workman in the Philadelphia General Hospital.

[6] Jour. Am. Med. Assn., May 9, 1914.
[7] Diseases of the Cerebrospinal and Sympathetic Nerves, Twentieth Century Practice.

I am unable to obtain any information that salvarsan or neosalvarsan had even been used in his treatment, and certainly his improvement and present condition were obtained before the recent methods of treatment were discovered, and there has been no serious relapse during a long period of years.

Syphilis affects not only the outer covering of the brain but also the lining of the ventricular spaces, and may produce intense lesions here. Proliferations of the ependyma may be great, and the aqueduct may be occluded in the same way as frequently is one of the brain arteries, and in this manner hydrocephalus may result. I have observed hydrocephalus confined to one posterior horn of a lateral ventricle or confined to the lateral ventricle of one cerebral hemisphere. A recent case in which hydrocephalus was confined to the posterior horn of one lateral ventricle occurred in the service of Dr. Mills. In studying the cause of this enlargement I found that syphilitic adhesions had formed in the middle of the ventricle, blocking off the posterior horn from the remaining ventricles.

W. H. entered the hospital June 10, 1913. He had been having left-sided headaches for six weeks, but had had right-sided convulsions nineteen years. The right retina was slightly swollen and the arteries were smaller than normal. The right field for white was slightly contracted. The left iris reacted very slightly to light; the left retina was swollen so as to make the edges of the vessels not so well defined as normal. The arteries were small, the veins larger than in the right eye. The left field for white was greatly contracted.

In July, 1913, left-sided symptoms had developed. Saliva dribbled from the left corner of the mouth, and the left side of the face showed paralysis, the left upper limb was weaker than the right, and patellar and Achilles reflexes were prompter on the left side, and the gait was that of left hemiparesis.

Dr. Holloway, about July 11, 1913, found there was no hemianopsia, but there was a tendency for deviation of the eyes to the right. It would seem as though this might have been because of defective vision in the right fields, especially as the patient's condition was such that accurate visual tests could not be made. Death followed an operation on the head. The necropsy was made July 24, 1913.

The examination showed much lymphocytic infiltration of the pia about the optic chiasm and at the base of the brain. The posterior and inferior horns of the left lateral ventricle were much dilated, but the anterior horn of this ventricle was of normal size. The right lateral ventricle was normal. Adhesions in the left lateral ventricle near the foramen of Monro doubtless were the cause of the occlusion of the posterior horn of this ventricle, and probably were of syphilitic origin. An area of softening was found in the outer part of the right lenticular nucleus extending into the brain upward, and probably was the cause of the left-sided symptoms of late develop-

ment. The cortex about the outer part of the dilated left posterior horn was not over 2 mm. in thickness at its narrowest part, and it is difficult to understand why right lateral homonymous hemianopsia was not produced.

Considerable infiltration of mononuclear cells in the pia of the medulla oblongata and chiasm and thickening of the vessels in the pia of the chiasm were found.

There are cases of syphilis with intense infiltration of mononuclear cells in the pia, such as is the common finding in nervous syphilis, and yet the clinical manifestations cannot be distinguished from those of tabes. Such a case is the following: A man, W. F. P., aged sixty-one years, was in my service at the Philadelphia General Hospital, and died there in 1911. He had a chancre when nineteen years old. About twenty years before he came under my observation his symptoms began with severe shooting pains in the lower limbs, and he became obliged to use a cane in walking. His eyesight began to fail about fifteen years before his admission to the hospital, and in about seven years he became blind. He had dribbling of urine. The Wassermann reaction of the blood was positive. The irides did not react to light, but did in convergence. He had loss of patellar reflexes, ataxic gait, diminution of touch and pain sensations, gastric crises, etc. It is not surprising that others as well as I regarded this case as a typical one of tabes.

The findings were intense infiltration of mononuclear cells in the pia of the spinal cord and of the chiasm and optic nerves, as well as of the chiasm itself. The optic nerves were intensely degenerated. Degeneration was seen in the posterior columns of the cord.

In tabes, as a rule, the infiltration of mononuclear cells in the spinal pia is slight, but death usually occurs late in the disease, and it is possible that the infiltration may have been pronounced in the early stage of the disease.

Of much clinical and pathological significance is the association of syphilis of the central nervous system with other lesions of this part entirely independent of the syphilitic process. I have reported a case in which I had made the diagnosis from the symptoms of tabes associated with syringomyelia, and the necropsy confirmed this diagnosis. A similar case had previously been reported by Schlesinger.

Recently, I[8] reported at a meeting of the Philadelphia Neurological Society a case in which the lesions of grave anemia of the spinal cord were associated with those of tabes.

In a symposium held at a meeting of the Philadelphia County Medical Society, September 27, 1916, I referred to the probability of certain cases of epilepsy having an origin in congenital syphilis, and mentioned that the examination of the family of a patient may

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[8] Spiller: Pennsylvania Med. Jour., November, 1916, p. 128.

indicate that the patient probably has congenital syphilis. I think it is well to repeat here verbatim the words used on this subject at that meeting. A brief report of this symposium has been published:

"Probably no one will dispute that syphilis may produce epilepsy, but there are some cases of epilepsy in which syphilis may only be suspected and not proved. I refer to cases in which a father has had a chancre before the birth of his child and the child becomes epileptic. Such a case has recently come under my observation. A man, aged twenty-seven years, has been epileptic since the age of seventeen years, and no cause can be determined. He had no convulsions in childhood, no severe head trauma, but the statement is made by the father that he had an initial lesion about twenty-three years before the birth of the son. The son shows no evidence of syphilis, his blood Wassermann is negative, and yet congenital syphilis may be the cause of the epilepsy. An elder brother had the notched teeth of hereditary syphilis."

Stoll[9] has published recently an interesting paper on "Hereditary Syphilis as a Cause of Chronic Invalidism," and states he judges that the diagnosis of hereditary syphilis by intensive familial study is not generally practised, as no mention was made of it in four symposiums which he recently attended in which many well-known syphilologists discussed the various problems of syphilis.

The subject of syphilis is a broad one, and many interesting features of this disease must of necessity be omitted in every symposium. I do not doubt that if the importance of family infection had been mentioned in these symposiums much information would have been forthcoming. It is certainly not rare for a physician to examine the near blood relatives of a patient with either congenital or acquired syphilis. Much has been written on congenital syphilis, and one would be remiss in his examination if in a case of suspected congenital syphilis he failed to investigate the patient's family.

Epilepsy is definitely caused at times by acquired syphilis, and it may be possible to trace the relation of cause and effect. In other instances of epilepsy the syphilis remains unrecognized. The Wassermann reaction may be negative, as it frequently is, when syphilis of the nervous system is of very chronic type. The following case, occurring recently in my practice, is illustrative of this point of view. A man, aged thirty years, began to have epileptic attacks at the age of twenty-five years, in the form of petit mal occurring at long intervals. Six brothers and sisters of the man were healthy, and there was no epilepsy in the family. He had been much exposed to syphilis, but had no knowledge of venereal disease. The Wassermann test of the blood was negative. In examining this man for symptoms of organic disease I found that he had delayed mic-

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[9] Jour. Am. Med. Assn., December 23, 1916.

turition; for a long time he had been unable to pass the urine unless the desire was very great, and he would stand for two to five minutes waiting for the urine to flow; he had lost sexual desire. The biceps and triceps reflexes were absent on both sides, the left patellar tendon reflex was very feeble, the right almost lost, and the Achilles reflexes were very weak.

There was not enough here to justify a diagnosis of syphilis, but there was enough to arouse a suspicion of this disease, and I urged the investigation of the spinal fluid and the cautious administration of mercury should the laboratory findings of the fluid be positive or even negative, because the infrequency of the attacks indicated a very chronic process compatible with negative laboratory findings.

It is often stated that syphilis of the central nervous system is a diffuse process implicating both brain and spinal cord. This usually is a correct statement. In a discussion on syphilis at the last meeting of the Congress of Physicians and Surgeons in Washington I called attention to the occurrence of focal syphilis of the central nervous system, in which the symptoms indicate that the lesion is confined to a very limited area. One of the most striking examples of this is a case of focal myelitis reported by me[10] in September, 1908. At that time we did not have the laboratory technic for the detection of syphilis we now possess. The occurrence of frequent attacks of "rheumatic pains," especially in the lower limbs, inequality of the pupils, loss of pupillary reaction, and a miscarriage at the fourth month suggest syphilis.

The case was one of hemiplegia. The muscles of the neck were rigid and voluntary movement of the neck was greatly impaired. Pain in the neck had been present about five weeks. Paralysis and rigidity of the muscles of the neck in hemiplegia are very extraordinary.

Microscopic examination showed small hemorrhages and swollen axis-cylinders in the third cervical segment. The small vessels in the cord had greatly thickened walls. Lymphocytic infiltration was found within the cord, and the nerve cells of the anterior horns were altered. The cord was less severely affected at the fourth cervical segment, and was about normal at the fifth cervical segment.

Usually when syphilis appears to be focal, careful examination will show further evidence of the disease, as in the two following cases:

Mrs. S., in September, 1915, complained of pain in the left buttock and left groin, and this pain became sharp and shooting in the left thigh. In March, 1916, the left lower limb began to be weak. In June, 1916, pain was noticed in the right lower limb, and at that time there was some rectal and vesical incontinence. When examined in July, 1916, the thighs and legs were distinctly wasted,

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[10] Spiller: Jour. Nerv. and Ment. Dis., September, 1908.

the right lower limb could be raised easily from the bed, but the left limb could not be raised from the bed or flexed at the knee, although movement of the toes was retained. Passive flexion of the left knee caused great pain. Sense of position was much impaired in the toes of each foot. Tactile, pain, heat, and cold sensations were almost lost in the distribution of the left first and second lumbar roots, and were diminished in the distribution of the twelfth thoracic and third lumbar roots. The patellar reflex was diminished on the left side and increased on the right side. Persistent ankle-clonus was present on each side. Lumbar puncture yielded a light green fluid, coagulating within two or three minutes, as in the Nonne-Froin syndrome. The cell count was 5. The blood Wassermann was strongly positive.

The symptoms-complex was clearly that of a lesion on the left side of the lumbar cord, implicating the 12th thoracic and the 1st, 2d, 3d, and 4th lumbar roots, and later the right side of the cord, probably by pressure. On account of the focal character of the symptoms I requested Dr. Frazier to perform an exploratory operation, and this he did. The dura showed a white opacity at the level of the first lumbar vertebra, and the tension was considerable, and the cord at this region was enlarged. The operation caused a complete cessation of the pains in the lower limbs.

In December, 1916, the woman was able to flex and extend the left lower limb, partially at the knee; both patellar reflexes were slightly exaggerated, and there was much more power in the left lower limb than there had been before the operation. She had received antisyphilitic treatment.

While so far this appears as a sharply focalized syphilitic lesion, information was elicited that before the symptoms began in the lower limbs there had been pains of short duration in the upper part of the left upper limb and in the left chest. This indicated that the process was a diffuse one.

In another case the patient, Mrs. P., about two years previously began to have sharp pains in the anterior part of the left thigh, and in about two months this pain yielded to numbness in this region. There had been also some numbness in the right hip. The patellar reflex was absent on the left side and diminished on the right side. The Achilles tendon reflex was absent on each side. Touch, pain, heat and cold sensations were lost in the anterior part of the left thigh. The blood Wassermann was strongly positive.

Here also was a case of focal syphilis, similar to that in the case just recorded, but further examination showed that headache had been severe, that diplopia and ocular palsy were present, and that paresthesia existed in the lower lip.

RESEARCHES IN REGARD TO THE COAGULO REACTION OF THE SYPHILITIC SERUM.

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THE Wassermann test was originally regarded as a specific serum reaction, dependent upon the interaction of antigen and antibody; but the extensive investigations which have since been devoted to this subject resulted in the conviction that the original assumption does not hold good, for it became apparent that lipoid extracts from non-syphilitic organs are as well adapted to demonstrate the reaction as the extracts of syphilitic livers which were employed at first. On the other hand, the extracts from cultures of spirochetes were shown by Noguchi's investigation to be not suitable for the purpose. A second hypothesis set up by Wassermann,[1] according to which in the course of syphilitic infection special antibodies to lipoids appear in the same organism, has also proved to be without foundation.

In addition to the Wassermann test a number of reactions are described which are more or less characteristic of syphilitic serum, and which consist mainly in precipitations which take place in the serum when certain additions are made to it. So far they have not proved very reliable as a means of diagnosing syphilis, since they occur far less regularly than the Wassermann reaction, and often have not the necessary accuracy and clearness.

A year ago Hirschfeld and Klinger[2] mentioned a new test which they christened the coagulo test, because it is built upon the technic of coagulation which they evolved. According to the data of the authors the results of this test are as characteristic as, and not less constant than, those of the Wassermann test. Subsequent experiments carried out by Frenkel and Thiele,[3] and especially by Brandt,[4] who tested a considerable quantity of material with the coagulo reaction, confirmed its utility for the diagnosis of syphilis. Brandt came to the conclusion that in many cases of treated or latent lues the Hirschfeld-Klinger test surpassed the Wassermann test in sensitiveness. From a theoretical point of view also the coagulo test is of interest, since it enables one to recognize the peculiar transformation undergone by the serum in the course of luetic infection on a totally different basis and by means of a widely differing technic.

[1] München. med. Wchnschr., 1913, p. 1331.
[2] Deutsch. med. Wchnschr., 1914, No. 32. Semaine méd., August 5, 1914.
[3] München med. Wchnschr., 1914, p. 2095.
[4] Deutsch. med. Wchnschr., 1915, No. 31.

Hirschfeld and Klinger[5] assume, in explanation of the reaction described by them, that ultramicroscopic precipitates produced by the extract in the serum (particularly in the globulins) enclose the lipoid particles and thereby render them ineffective for coagulation. While the Wassermann test only demonstrates these globulin precipitations indirectly by means of the alterations they induce in the complement, the coagulo test enables one to recognize them at once by the lipoids which participate directly in the process; this circumstance establishes the superiority of the coagulo reaction to the Wassermann reaction.

In this paper I wish to report upon a considerable number of cases which I investigated by means of this new test, comparing, at the same time, my results with those of the Wassermann test. I also experimented whether, by altering the dose of the separate agents, the delicacy of the test could be heightened without its specificity being diminished.

Perhaps I may be permitted to preface my report by a few general facts on the physiology of coagulation which are necessary for the thorough comprehension of what follows:

When blood coagulates two separate processes can be distinguished, namely, the development of thrombin (fibrinferment) and the precipitation by the thrombin of fibrinogen, i. e., the actual coagulation (or formation of fibrin). The thrombin itself consists of two substances, (1) the serocym (thrombogen), which is an albuminous constituent of the blood plasma, and (2) the cytocym (thrombokinase), which belongs to the group of the lipoids, in particular of the lecithins, and which can be extracted from almost any cells by means of alcohol. In the blood one of the chief sources of the cytocym are the blood plates, by the decomposition of which the cytocym requisite for the coagulation of the blood mainly becomes free. If ionized calcium salt is present the serocym and cytocym form thrombin. Once the latter has developed it occasions the precipitation of fibrinogen even in the absence of Ca ions, for instance in oxalate medium. The accompanying scheme will present the processes clearly.
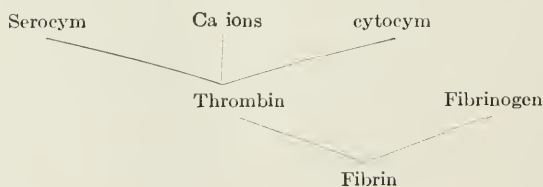
If, therefore, we wish to prove the presence of thrombin in a fluid and to determine its quantity, we only require to mix a definite amount of this fluid with a solution of fibrinogen and to observe when

[5] Ztschr. f. Immunit., 1915, xxiv.

coagulation takes place. This process ensues the more quickly the more thrombin is present, and does not occur at all without thrombin.

In place of the too unstable pure fibrinogen solutions there may with advantage be employed, according to the investigations of Bordet and Delange, a weak solution of oxalate plasma, i. e., plasma obtained by centrifugation of blood mixed with oxalate. Upon the addition of larger quantities of thrombin this oxalate-plasma hardens in from one to two minutes; smaller quantities only cause coagulation after eight to fifteen minutes, whereas mere traces of thrombin only cause incomplete coagulation in the course of several hours. The employment of plasma mixed with oxalate has not only the advantage that this plasma (fibrinogen) solution will keep good a long time, but it also prevents any further formation of thrombin from the moment at which the plasma is added. The reason of this is that the Na oxalate precipitates the lime in the form of insoluble Ca oxalate, and the consequent lack of Ca ions renders any further formation of thrombin impossible. We are thus enabled to determine quantitatively the amount of thrombin present in a fluid at a given moment, also the process of coagulation is divided into two distinct phases, that of the formation of thrombin and that of the proof of thrombin being present, a methodological advance which the physiology of coagulation owes to the researches of Bordet and Delange.

We have seen in the above how thrombin can be determined quantitatively. But for the coagulo test we must be able to measure accurately not only the resulted thrombin, but also one of its constituents, the cytocym. To attain this aim the procedure is as follows: We add to the fluid of which the cytocym content is to be determined a solution of serocym (sheep serum) and a small quantity of CaCl$_2$ solution, both in carefully ascertained amounts. If cytocym is present the formation of thrombin will immediately follow, which will have reached its height in ten to fifteen minutes, and which will be the more vigorous the more cytocym is present. After fifteen minutes we interrupt the formation of thrombin by the addition of oxalate plasma. The thrombin which has formed will cause the coagulation of the latter, which process will be the quicker the more abundantly thrombin had formed. The time required for coagulation is therefore in inverse ratio to the amount of thrombin, i. e., of cytocym.

This method enables one to determine the quantity of coaguloactive lipoids (cytocym) in a fluid not indeed absolutely but yet very exactly in relation to a given cytocym solution. In this quantitative measurement of cytocym we see demonstrated the technical side of the coagulo test described by Hirschfeld and Klinger.

The principle of this test is based upon the fact that most of the alcoholic organic extracts which are employed for the Wassermann test, when emulsionized in the customary manner in saline solution,

provide good cytocym, and that the coagulating activity of these extract emulsions is greatly depressed or even wholly arrested by syphilitic sera, whereas normal sera only influence it very slightly. The line of action to be pursued, therefore, consists mainly in digesting for some time a suitable quantity of the serum to be examined with the extract in emulsion, then determining the cytocym content, *i. e.*, the coagulating activity of the extract by comparing it with the activity shown by the same quantity of extract after it has been in contact with normal serum or with saline solution.

TECHNIC. In regard to the preparation of the reagents required for this test the following observations may be of use:

1. *Extract Emulsion.* Only alcohol, not acetone extract, can be employed. Almost every extract may be employed. We generally made use of extracts taken from guinea-pigs' hearts or the human liver. The concentration and effectiveness of the extract should be such that, diluted twenty to forty times and tested in the manner described below, 0.1 c.c. of it causes the oxalate plasma to coagulate in one to three minutes. Of this extract, which can be preserved for an unlimited period if it be kept unpolluted by water (for example, wet pipettes), dilutions should be made of 1 to 40, 1 to 80, 1 to 160, even 1 to 320 in saline solution and 0.1 c.c. of each of these dilutions decanted into glass tubes ready for each serum that has to be examined. Should an extract in a given concentration not be sufficiently active it can be concentrated somewhat more by vaporization of part of the alcohol; it is not advisable to employ for the coagulo reaction extracts the effect of which is too weak. The use of more powerful extract concentrations than those cited above (for instance, 1 to 10) is not permissible on account of the alcohol which affects the formation of thrombin. Considering the extraordinary activity of most organic extracts it is usually easy to procure them in the strength which seems most desirable.

2. *Serocym.* According to Hirschfeld and Klinger the most serviceable serocym solution is sheep or goats' serum, prepared from the oxalated blood of these animals in the following way: From the compressed jugular vein blood is drawn off in a jet, not drop by drop, by means of a fairly thick cannula and conducted into a glass retort containing 1 per cent. Na oxalate solution. As this solution is not isotonic for all animals we recommend adding to it one-twentieth volume of a 10 per cent. saline solution. The blood is allowed to flow into the retort until it reaches a certain mark made beforehand on the latter, and which shows that the blood now contains 1 per mil. oxalate, *i. e.*, the oxalate solution has been diluted ten times over by the blood. During the process of taking the blood everything must be avoided which might favor the formation of thrombin. The blood as it flows into the retort should be shaken slightly so that it mixes immediately with the oxalate. It is important that the con-

densation of water vapor from the warm blood on the glass walls of the retort be prevented, as otherwise partial hemolysis easily occurs, the plasma becomes red and is consequently useless. This condensation can be sufficiently arrested by heating the oxalate solution and the retort to about 40° C. and thoroughly moistening the inner walls of the retort with the blood as quickly as possible. Blood obtained in this manner does not coagulate and must next be centrifugated in centrifugal glasses which have been previously rinsed in saline solution (this again to avoid condensation); after ten to fifteen minutes the plasma, now free from blood, must be pipetted off into fresh glasses and vigorously centrifugated for at least a half hour in order to remove the blood plates. The resulting plasma should be absolutely clear, and if colored at all, of a yellow shade, by no means reddish. From it we procure the serum serocym by means of recalcification to produce coagulation. We add one-tenth volume of a 1 per cent. $CaCl_2$ solution, which causes the whole to become much clouded, and leave it to stand for a quarter hour, preferably in a temperature of 37° C. The plasma coagulates during this time and must now be taken hold of by one side with long forceps (about 35 cm. long) and pressed dry by a wringing movement. If the plasma has not coagulated at all, or only partially after the lapse of ten to fifteen minutes, the addition of a few more drops of $CaCl_2$ solution usually suffices to bring about rapid coagulation. Plasmas which will not coagulate at all, or only do so very slowly in spite of a sufficient addition of Ca (and this often happens in the case of plasma which have been kept for some time), often do not produce usable serocym at all. After being pressed dry the serocym must be left to stand for some time. It then frequently coagulates again, in which case it must be pressed dry again. Freshly dried serocym still contains a little thrombin, so should not be used for testing purposes until after the lapse of one to two hours. For the tests it must be diluted with five times its volume of physiological saline solution and employed in the proportion of 0.5 c.c. per tube. Good serocym should contain neither cytocym nor thrombin. For every test it must be controlled in this direction. The dose to be employed must be put into the tube with the $CaCl_2$ without cytocym, and, mixed with oxalate plasma, should not coagulate, at least not until the following day. The procuring of good serocym is the only preparation in connection with the coagulation test, which is attended by some slight difficulty. But after a little practice it becomes quite easy to procure serum of the required quality. Certainly it may occur that serocym which has been obtained with all due observance of rules and regulations is nevertheless ineffective, *i. e.*, only generates in conjunction with the cytocym a small amount of thrombin. The primal cause of this phenomenon is not yet fully clear. Experiments which I made in this direction showed that the

serocym content of the blood not only varies from animal to animal, but is even subject to variation in one and the same animal; nor could I discover that this occurrence has any connection with any physiological process, such as digestion, etc. Often blood which had been taken from a sheep in the afternoon was very rich in serocym, while a specimen taken in the morning had only provided very inferior serocym. Many sheep have habitually such inferior serocym that their blood cannot be employed for illustrating the reaction. Weak serocym can be considerably improved by leaving it to stand for some hours in ten times the volume of distilled water instead of immediately adding saline solution to it as directed above. Before the solution (it will be cloudy on account of the globulin precipitate) can be used, 10 per cent. saline solution must be poured into it until it contains 0.8 per cent. of salt, after which it may be employed in doses of 1.

Serocym taken from other animals in use in laboratories is less well adapted for our purpose; rabbits, indeed, provide serviceable serocym, but it would be difficult to procure it in the required quantity. Guinea-pigs, oxen, and human beings have not a sufficient amount of serocym.

3. *CaCl₂ Solution.* This is a physiological saline solution to which are added 5 per cent. of a 1 per cent. CaCl₂ solution.

4. *Oxalate Plasma.* For this the oxalate plasma designed to provide the serocym can be used, but as it must be available in considerable quantities it is advisable to obtain the blood of some large animal in oxalate direct from the incision (1 per cent. oxalate). It must be centrifugalized twice over as soon as possible to remove all the blood plates. Frequently when plasma obtained in this manner has stood for one to two days, coagula appear in it, caused by small amounts of thrombin reaching the blood in spite of all precautions. These coagula, which may not be too copious, must be strained off by filtering (through cotton-wool) until the plasma should be quite clear; if this is the case it can be preserved fit for use for one or two weeks if kept in a refrigerator. When in use it must be diluted as follows: 1 part plasma, 5 parts physiological saline solution, ½ part 1 per cent. Na oxalate solution. In the following this mixture will merely be designated oxalate plasma.

5. *Preparation of the Serum.* Some of the patient's blood must be collected in a centrifuge tube and treated in the same manner as for Wassermann test. The serum must be well centrifugated and should not be tinged red to any appreciable degree by dissolved corpuscles (see below). As the serum resulting from the spontaneous coagulation of blood always contains a certain amount of cytocym, which would disturb the coagulo reaction, the sera intended for the test must be thoroughly inactivated; preferably for an hour in a temperature of 56° C., whereby the cytocym of the serum will be destroyed.

Carefully handled, sera are usually free of cytocym after heating for half an hour; unskilfully obtained specimens of blood, on the other hand (such as have been violently shaken on the transit for instance), produce sera that are very rich in cytocym, and consequently require to be heated for an hour up to 58 or 60°C.

DEMONSTRATION OF THE REACTION. The coagulo test can be carried out most conveniently by using a stand in which can be placed a considerable number of tubes in rows, each row containing four or five tubes. Each serum must be tested with three or four different doses of cytocym. A corresponding number of dilutions of the organic extract (see above) must be prepared, for instance, in the proportion of 1 to 40, 1 to 80, 1 to 160, and 1 to 320. Of each of these 0.1 c.c. must be decanted into a separate tube and 0.1 c.c. eventually 0.2 c.c. (see below) of the inactive serum added to it.

For the control the same dose of the serum alone (without the extract) must be left to stand in 0.1 saline solution; similarly the doses of extract employed must be placed in the control tubes alone, i. e., without the addition of serum. The tubes must next be well shaken and then left to stand half to one hour at room temperature. During this time the reaction between serum and cytocym will take place. At this stage of the procedure we add to the contents of each tube, including the controls, 0.5 c.c. of the serocym dilution and 1 c.c. $CaCl_2$—NaCl solution; mix them thoroughly and again leave the tubes to stand for fifteen minutes (formation of thrombin). At the end of this time 1 c.c. oxalate plasma must be added everywhere, mixed at once with the other contents and the time of coagulation noted. If the reagents have been skilfully placed in the tubes and the serocym is good the controls should coagulate after one or three to five minutes; negative sera postpone the time of coagulation for some minutes while positive sera definitely inhibit coagulation. The control containing serum alone should remain liquid, as here no cytocym was added; if one of these tests also coagulates (autocoagulation) it is a sign that the serum itself still contained some cytocym (probably through being unskilfully procured). Such sera are useless for demonstrating the coagulo reaction. This autocoagulation has nothing in common with the auto-inhibition which occurs sometimes when the Wassermann test is applied, for if a second specimen of the same ·patient's blood is taken and more carefully handled the serum can always be used.

Below I insert two protocols of experiments which illustrate the times of coagulation characteristic for positive and negative sera. From them it is apparent that not every dose of cytocym affords serviceable figures, for, proportionate to the strength of the serocym, etc., sometimes the larger, sometimes the smaller, amounts of cytocym furnish the determining factors for a diagnosis.

PROTOCOL I.

Extract dilution.	Extract without serum.	Control sera. +	Control sera. −	1	2	3	4	5	6	7	8	9	10
1: 40	1½'	5'	2½'	3½'	3½'	2½'	1½'	5'	2'	2'	30'	2½'	2'
1: 120	2'	30'	4'	2½'	fl.	3'	3'	fl.	2'	3'	fl.	30'	3½'
1: 240	2'	fl.	5'	fl.	fl.	15'	4½'	fl.	3'	5'	fl.	fl.	4½'
Serum without extract	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	5'
Result				±	+	±		+			+	+	A
W. R.				+	+	?		+			+	+	+
Clinical diagnosis:				Iritis.	Iritis.	Orchitis.	Syphilis.	.....	Lues latens.	Lues III.	Lues III.	Progressive paralysis.	Lues III.

PROTOCOL II.

Extract dilution.	Extract without serum.	Control sera. +	Control sera. −	1	2	3	4	5	6	7	8	9	10
1: 40	1'	2'	1½'	1½'	2½'	2'	3'	1½'	2'	3'	1½'	2'	1½'
1: 80	1'	5'	2'	2'	5'	4	22½'	2'	2'	5'	2'	2'	2'
1: 160	1½'	15'	3'	3'	18'	15'	fl.	3'	3'	14'	4'	3'	4'
Serum without extract	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.
Result					+	+	+			+			
W. R.					+	+	+			+			
Clinical diagnosis:				Lues latens.	Lues I.	Lues latens, treated.	Tabes dorsalis.	Neurasthenia.	Tabes dorsalis, incipient.	Progressive paralysis.	Lues latens, treated.	Paranoia.	Wet-nurse.

W. R. = Wassermann reaction.   fl. = fluid.   + = positive.   ± = weak positive.   A = autocoagulation.

PROTOCOL III.—A. PRELIMINARY ARRANGEMENT.

Extract dilution.	Extract without serum.	Positive serum, 0.1 c.c.	Weak positive serum, 0.1 c.c.	Negative serum, 0.1 c.c.
1: 40	2'	15'	7'	4'
1: 120	4'	30'	20'	6'
1: 240	6'	45'	30'	15'
Serum without extract	fl.	fl.	fl.	fl.

PROTOCOL III.—B. PRINCIPAL REACTION.

Extract dilution.	Extract without serum.	1 0.1	1 0.2	2 0.1	2 0.2	3 0.1	3 0.2	4 0.1	4 0.2	5 0.1	5 0.2	6 0.1	6 0.2	7 0.1	7 0.2	8 0.1	8 0.2	9 0.1	9 0.2	10 0.1	10 0.2	11 0.1	11 0.2
1: 40	2'	2'	4'	3'	5'	1h	fl.	4'	6'	2'	5'	2'	3'	3'	3'	3'	3'	2'	5'	2'	5'	2'	5'
1: 120	4'	1h	fl.	16'	fl.	fl.	fl.	5'	30'	12'	20'	4'	5'	16'	18'	10'	45'	6'	18'	4'	6'	5'	8'
1: 240	6'	fl.	fl.	fl.	fl.	fl.	fl.	25'	fl.	30'	fl.	7'	11'	18'	30'	15'	fl.	fl.	fl.	6'	12'	fl.	fl.
Serum without extract	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.
Results				‡	‡	+++								‡	‡								
W. R. o		+																					
W. R. n																							
Clinical diagnosis:		Lues II, treated.		Tabes dorsalis, treated.		Lues ?		Phthisis, pulmonary.		Tumor at tonsilla.		Lues healed.		Lues.		Polyneuritis.		Iridocyclitis.		Keratitis.		Irido-cyclitis.	

W. R. o = means old methods; W. R. n = new method (see below).

In Protocol I the positive sera (third row of tubes) have completely destroyed the cytocym of the smallest dose of extract ($\frac{1}{240}$). A slightly positive serum, No. 3, responding uncertainly to the Wassermann test, coagulates in fifteen minutes, while the time required by the negative sera is only three to five minutes (in conjunction with extract alone four minutes). With a double quantity of extract the difference is still clearly discernible with the exception of Nos. 3 and 10, when they can no longer be sufficiently distinguished. The first row, on the other hand, containing one-fortieth extract, does not furnish figures serviceable for differentiating between positive and negative.

In the second protocol the serocym was still stronger, the gradation of the doses of extract not being carried so far. The positive sera consequently did not cause absolute inhibition, but only a protraction of the time equaling ten to fifteen minutes. In the second row the differences are just intimated, in the first scarcely recognizable.

The third protocol illustrates the furthest extreme in the opposite direction. Here the serocym was so weak that in the third row even many negative sera (like Nos. 4 and 5) caused considerable delay in the time of coagulation. Most of the tubes in this row remained liquid. Here diagnosis must be based on the second row, where the time limit for positive sera is fifteen minutes. In the first row only the positive sera (positive in response to the older style of Wassermann test) show definite results.

We shall refer again to the figures contained in this table, which were obtained with 0.2 c.c. serum.

To this protocol is prefixed a preliminary experiment which was carried out in the morning to test the reliability of the serocym prior to the demonstration of the principal reaction (of which protocol III B only reproduces a small part). Since it sometimes happens, as already mentioned, that the serocym only causes very slight formation of thrombin, it is advisable to determine each time its quality. The serocym, diluted 1 to 4, must be placed in the tubes in a dose of 0.5 c.c., together with doses of extract, arranged in a falling scale, eventually also with a positive and a negative serum; according to the thus ascertained strength of the serocym the doses of extract can be more or less graduated in the main experiment. To guard against failure when experimenting on a large scale it is well to employ four rather than only three different doses of extract (1 to 40, 80, 160, 320), even though this precaution necessarily rather increases the number of tubes.

The inserted protocols seem to make it clear that the difference between positive and negative sera is only quantitative. In the case of the coagulo test (just the same as when the Wassermann test or any other test based on serum reaction is applied) only positive sera cause the appearance of definitely typical signs (such

as the plasma remaining fluid instead of coagulating), while the numerous slightly positive sera, or such as show a mere trace of luetic infection, can only be classified by the help of collateral comparisons and special reflexion. It is necessary, therefore, always to experiment simultaneously with a positive and a negative serum, and especially to employ some slightly positive sera as controls, after which a careful comparison of all the results must take place. It is also desirable always to apply the coagulo test to a considerable number of sera at once, as it is then far easier, especially with the additional help that may be afforded sometimes by the anamnesis of particular patients, to decide upon the border cases, whether they are to be ranked as negative or just positive.

Altogether I subject to the coagulo test 500 sera which had been sent to the institute for examination by the Wassermann test and compared the two sets of results. The *résumé* in Protocol IV shows how this material was classified in accordance with the clinical aspect of the respective case, and to which extent the results of the two methods of testing coincided.

Agreement between the two reactions under comparison was attained in 92.75 per cent. of the cases if we do not exclude cases where merely the strength of the reactions differed ($+$ and $=$). In regard to the remaining 7.25 per cent. the coagulo test cannot be said to have failed throughout, since a number of cases belong here in regard to which the anamnesis supports the testimony of the coagulo test rather than of the Wassermann test and thus establishes the superiority of the former to the latter (positive, generally $\pm$) according to coagulo test, negative according to Wassermann test in 13 cases of treated lues and suspected lues, in 5 cases of latent lues, and in 12 cases in which the anamnesis indicated other symptoms of syphilis). On the other hand there were only 8 cases which resulted negatively in the coagulo test, while the clinical aspect and the Wassermann test pointed to syphilis. In the case of these few sera (as in that of the autoprecipitations), in all probability, not the coagulo test as such was at fault, but awkwardness in the method of procuring and despatching the specimens of blood, an important factor to which we shall again refer.

If we only include those cases in which the clinical aspect pointed to probable lues (269 cases) the coagulo test was positive in 173 cases (64.7 per cent.) and the Wassermann test only in 154 cases (57.2 per cent.); this signifies a superiority of the former on the latter of 7.5 per cent.

In explanation of the table under the title of "various affections" were examined, among others, one case of psoriasis and one of lichen, both negative. One case which clinically was described as sporotrichosis was positive both in the coagulo and in the Wassermann test, and therefore doubtless of syphilitic origin. Among the group of wet-nurses were 2 cases which reacted slightly positively in the

coagulo test, though they responded negatively to the Wassermann test and had no mention of lues in their record. The serum of women before and after childbirth also showed in some cases a certain tendency to inhibit the activity of cytocym more than other normal sera, but always only in a limited degree. Similar observations have been made in patients suffering from tumor, for instance, in a case of tumor on the kidney, which is included in the table. Whether in these two conditions positive coagulo reaction really occurs frequently can only be proved by further careful investigation.

PROTOCOL IV.

Clinical diagnosis.	Reaction.	Positive.	Weak positive.	Negative.	Number of cases.	Conform-able.
Lues I	W.	6	3	8	17	16
	C.	5	5	7		
Lues II	W.	18	5	20	43	42
	C.	17	5	21		
Lues III	W.	11	2	5	18	18
	C.	9	4	5		
Lues	W.	17	0	23	40	39
	C.	16	2	22		
Lues latent	W.	8	8	34	50	47
	C.	8	11	31		
Lues treated	W.	7	2	38	47	43
	C.	8	3	36		
Lues hereditary	W.	2	1	5	8	7
	C.	2	2	4		
Lues cerebral	W.	0	0	4	4	3
	C.	1	0	3		
Tabes dorsalis	W.	6	1	7	14	13
	C.	6	2	6		
Progressive paralysis	W.	9	0	4	13	12
	C.	9	1	3		
Lues, questionable	W.	21	10	77	108	104
	C.	20	15	73		
Iritis, iridocyclitis	W.	4	0	13	17	14
	C.	4	3	10		
Keratitis parenchymatosa	W.	4	0	3	7	7
	C.	3	1	3		
Non-syphilitic eye diseases	W.	0	0	9	9	9
	C.	0	0	9		
Indefinite syphilitic diseases of central nerve system	W.	0	0	12	12	10
	C.	1	1	10		
Clinical, not syphilitic infectious diseases	W.	0	0	9	9	9
	C.	0	0	9		
Aortic insufficiency	W.	0	1	4	5	5
	C.	1	0	4		
Tumor	W.	0	0	5	5	4
	C.	0	1	4		
Chronic nephritis	W.	0	0	3	3	3
	C.	0	0	3		
Pulmonary tuberculosis and lues	W.	2	1	2	5	4
	C.	2	2	1		
Tuberculosis	W.	0	0	7	7	6
	C.	1	0	6		
Lupus	W.	0	0	1	1	1
	C.	0	0	1		
Addison's disease	W.	0	0	1	1	1
	C.	0	0	1		
Anemia	W.	0	0	3	3	3
	C.	0	0	3		
Faults of hearing	W.	0	0	6	6	5
	C.	0	1	5		
Various affections	W.	1	0	16	17	17
	C.	1	0	16		
Diseases without diagnosis	W.	4	2	14	20	20
	C.	3	3	14		
Diabetes mellitus	W.	0	0	4	4	4
	C.	0	0	4		
Wet-nurse	W.	2	0	13	15	13
	C.	2	2	11		
Healthy	W.	0	0	3	3	3
	C.	0	0	3		

W = Wassermann reaction.   C = coagulo reaction.

The sensitiveness and accuracy of the coagulo test are dependent in the first instance from the amount of cytocym employed. By graduating the dilutions of extract more elaborately than Hirschfeld and Klinger originally suggested (the second and third row of tubes now contained instead of $\frac{1}{2}$ and $\frac{1}{4}$, $\frac{1}{3}$ and $\frac{1}{6}$ of the dose of extract employed in the first row) I succeeded in intensifying the sensitiveness of the coagulo test still further. This is obvious at once if we compare it with the Wassermann test results. Brandt, who worked with less diluted cytocym, attained agreement between his results and those of the Wassermann test in 94 per cent. of the cases under examination.

He had compared his results with those of the Wassermann test as it was carried out at that time in the institute[6] according to the scheme in general use (0.1 serum, 0.05 complement, three different extracts in single and double, not autoinhibiting doses). Meanwhile a change of technic was introduced in the institute which, judging from our experiences up to the present time, increased the sensitiveness of the Wassermann test by about 10 per cent.

Starting from the well-known fact that hemolysis takes place more quickly in the tubes containing negative sera plus extract than in the controls containing extract alone, Frenkel (in Heiden) suggested going a step further: employing the extract in an auto-inhibiting dose and adding to it relatively large amounts of serum (up to 0.5 c.c.). Negative sera prevent autoinhibition while positive sera increase it.

I compared my results with those afforded by this elaborated complement-binding test which, as mentioned above, in cases of syphilis furnishes positive results about 10 per cent. more frequently than the old method. As, even after this innovation, I attained agreement between the coagulo test and the Wassermann test quite as often as Brandt (94 per cent.), this would seem to prove that the further the graduating of the extract doses is carried the more sensitive is the test.

In a number of experiments I tried putting larger doses of the serum under examination into the tubes as well as the customary quantity (0.1), and investigated whether by this means more definite results might be reached in slightly positive or questionable cases. The greater the quantity of serum added to a constant dilution of cytocym the less effective the latter becomes for the coagulo test. 0.1 c.c. of normal serum compared with the control (saline solution) almost always shows delay of coagulation for some minutes. If 0.2 to 0.5 c.c. serum are employed the delay is far more pronounced. No increase in the sensitiveness of the reaction on luetic sera was observed in general as a result of employing these larger amounts of serum (see for instance Protocol III, for which all the sera had been

[6] He also made his investigations in the institute of Hygiene at Zurich.

tested in double as well as the ordinary quantities). If the doses of serum amount to 0.3 c.c. or more, even normal sera not infrequently show apparently positive results; with doses of 0.2 c.c. the reaction was in some cases more sharply defined than with 0.1 c.c. In other experiments this was not the case, the interpretation of the results was, on the contrary, sometimes rendered more difficult by unspecific inhibition being observed in normal sera. It seems best, consequently, to apply the test with 0.1 c.c. of serum. In experiments with only a few sera I would suggest filling a second row of tubes with the 0.2 c.c. dose of each serum.

PROTOCOL V.

Clinical diagnosis.	Lues, infection one year ago.		Lues 11.		Lues 1-II.		Ulcer of anus.		Acute otitis.		Ulcer on penis.		No diagnosis.		Extract without serum.
W. R.	$+$		$+$		$+$		$-$		$-$		$-$		$-$		
	a	b	a	b	a	b	a	b	a	b	a	b	a	b	
Extract dilution:															
1: 40	2′	2′	3′	2′	3	3	1′	1′	1′	1′	1′	1′	1′	1′	1′
1: 80	3′	3′	3′	3′	14	3	1′	1′	1½′	1′	3′	1′	1′	1′	1′
1: 160	4′	4′	12′	3½′	15	3½	3½′	3′	3′	2′	5′	3′	1½′	1′	1′
1: 320	fl.	5′	15′	5	fl.	5	1½′	4′	10′	4′	25′	10′	4′	2′	2′
Serum without extract . .	fl.	5′	fl.	fl.	l.	fl.	l.	fl.	l.	fl.	fl.	fl.	fl.	5	fl.
Results	$+$	A	$+$	$-$	$+$	$-$	$-$	$-$	$-$	$-$	±	$-$	$-$	A	

Series a = without the addition of blood.
Series b = with the addition of blood.
A = autocoagulation.
W. R. = Wassermann reaction.

In the course of our experiments we were struck by the fact that the sera which reacted slightly positively in the Wassermann test and negatively in the coagulo test were often colored a deepish red by hemoglobin. This led us to investigate whether the admixture of small definite quantities of dissolved blood could affect the sera in such a way as to diminish their inhibition in regard to cytocym. This is actually the case, as the following protocol shows. For the practical illustration of this phenomenon it is necessary to add the blood to the serum before the latter is inactivated and then to heat the two together. The reaction is not affected if blood, heated separately, is added to the serum after its inactivation. Also, the quantity of blood must not be too great, as then, on account of the lipoids content of the blood corpuscles, the serum becomes too rich in cytocym, which in its turn leads to autoprecipitation (Nos. 1 and 7 in the protocol).

Both positive and negative sera, as classified by the Wassermann test, should be inactivated after the customary manner, some with and some without the addition of 1 to 3 drops of washed human blood corpuscles (a 5 per cent. suspension in saline solution), and then subjected to the coagulo test.

The result shows that in every case in which blood was added

inhibition was lowered, a condition which would require us to declare serum heated together with blood as no longer positive, but negative.

I wish to lay particular stress on this source of possible errors (which has been overlooked by earlier investigators), because sera more or less tinged with red in consequence of the blood having been carelessly drawn, or the specimen violently shaken on the transit are not all uncommon and might occasionally account for the fact of a slightly positive reaction in a serum not being registered by the coagulo test.   If the latter were applied to irreprovable material only I doubt if it would ever fail.

SUMMARY.   In summarizing the results of my investigations I may safely assert that the coagulo reaction is highly characteristic in the case of syphilitic serum, especially when the elaborated method described above is applied, and the sources of possible mistakes which we have also mentioned carefully avoided.   In many cases this test is distinctly superior to the Wassermann reaction. After some practice one easily gains sufficient mastery over the technic on which it is based to be able to examine even a large number of sera without difficulty.   It is hardly probable that the coagulo reaction will finally supercede the time-honored Wassermann reaction; but it does seem calculated both to furnish scientific research with valuable data in regard to the transformation of serum as wrought by syphilis, and also to facilitate the diagnosis of doubtful cases of syphilis, possibly also of certain apparently similar conditions.

THE NERVOUS SYMPTOMS OF POLYCYTHEMIA VERA.[1]

BY HENRY A. CHRISTIAN, M.D.,

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IT seems worth while to emphasize the nervous symptoms presented by patients with polycythemia vera, not because the case reports and various studies of this condition fail to make mention of their frequent occurrence, but because a failure to keep them in mind very often has led to diagnostic mistakes and in some instances to cerebral operations, with the idea that the symptoms were the result of brain tumor.

If one has in mind the very striking appearance of some patients of this group with their marked cyanosis or, probably better, reddish cyanosis it would seem as if this disease would be recognized promptly; but, alas, how often do we fail to see what is just in front

[1] Read at the meeting of the Association of American Physicians, May, 1917.

of our eyes because with vision is not combined thinking and the application of experience acquired by previous observation and reading. Then too sometimes patients with polycythemia vera are neither abnormally blue nor red. In fact, occasionally they may be pale. As Osler pointed out in his paper on "Erythremia or Polycythemia with Cyanosis," in 1908,[2] there may be much variation in the color of people depending on the condition of the cutaneous vessels and the rate of blood flow. If the capillaries are full and the flow slow, cyanosis predominates; if the current is rapid an arterial color is prominent. In polycythemia usually there is a definite mingling of the two colors resulting in what might be termed a red cyanosis. These variations are strikingly evident if the changes produced by warmth or cold or by changes in position of an extremity are noted in the same patient. What is particularly important from the point of view of diagnosis is that the skin in patients with polycythemia sometimes may show pallor due presumably to vasoconstriction or peripheral circulatory failure, and in these cases the diagnosis is likely to be missed unless a blood count or the finding of an enlarged spleen point the way.

The nervous symptoms are various. Vaquez's[3] original case had vertigo, buzzing and whistling in the ears, and paroxysms of dizziness. Osler,[4] in his report, which aroused interest in the subject, and which in America and England has been in large part responsible for the general recognition of this condition as a disease entity, describes 4 cases which he himself observed, and collects 5 others from the literature. Of these 9 case reports all except 1 contain mention of nervous symptoms, such as vertigo, fulness in the head, headache, pain and prickling sensations in the extremities, ringing in the ears, loss of consciousness, thickness of speech, staggering gait, muscle weakness, blurring of vision, etc. Senator[5] in his excellent little monograph *Polyzythemie und Plethora* begins his description of symptomatology, etc., by saying that subjective symptoms usually occur, due to the overfilling of the bloodvessels and the abnormal composition of the blood, such as giddiness, rush of blood to the head, flashes of light, migraine-like attacks of pain in the head, etc.

A brief *résumé* of 10 cases of polycythemia, which I have had opportunity to study on my services at the Carney and Peter Bent Brigham Hospitals, or that of my colleague, Dr. Cushing, on the surgical service at the Peter Bent Brigham Hospital, will serve to illustrate the frequency and importance of nervous symptoms in these patients.

CASE I.—Female, aged fifty-one years, was admitted to the medical service of the Carney Hospital March 15, 1911. Nervous

[2] Osler: Lancet, 1908, i, 143.   [3] Compt. rend. Soc. de biol., 1892, 384.
[4] AM. JOUR. MED. SC., 1903, cxxvi, 187.
[5] Verlag v. August Hirschwald, Berlin, 1911.

symptoms were frequent headaches; sharp, shooting pains through the head, face, and back of neck; attacks of transient blindness; at other times blurring of vision. Many of these symptoms were present for eight years before admission, during which time her red blood count ranged between 7,512,000 and 10,616,000. Her color was usually cyanotic. She came to the Carney Hospital with abdominal symptoms. At this time the only deepening of color noted was a slight cyanosis of the fingers, though her red blood count was 8,500,000. She died two days after admission and autopsy showed thrombosis of the portal vein and its branches; infarction of the small and part of the large intestine; splenomegaly. Permission to examine the brain could not be obtained.

CASE II.—Male, aged fifty-five years, was admitted to the medical service of the Carney Hospital April 18, 1911. No nervous symptoms of a definite nature. No cyanosis or erythema noted. Red blood counts: highest, 8,224,000; lowest, 6,752,000.

CASE III.—Female, aged forty-five years, first came to the medical outdoor department of the Peter Bent Brigham Hospital April 26, 1915. Her nervous symptoms were dizziness, faintness, nervousness, difficulty in sleeping, and disturbance of vision, although repeated eye examinations have shown no visual defect. Her color was a reddish cyanosis or congestion, particularly evident in face and neck. Her hemoglobin ranged between 107 per cent. and 112 per cent., and her red blood count between 5,270,000 and 5,620,000.

CASE IV.—Male, aged fifty-five years, was admitted to the surgical service of the Peter Bent Brigham Hospital September 29, 1915. Nervous symptoms were recurring headaches of twenty years' duration; for ten years had eye symptoms consisting of fatigue and poor vision scintillating scotomata, and blind spots in his fields of vision; for six years recurring sensations of tingling in the left arm and leg, to which, in June, 1915, was added transitory weakness of the left arm, causing a wrist-drop, and in August, 1915, sudden complete paralysis of the left arm, which lasted for twenty-four hours. Ten days before admission he began to have severe headache and paresthesia of the left side of his body. Then his left arm became weak, so that four days ago he carried it in a sling and was unable to use his fingers or move his wrist. At this time the muscles in his left arm occasionally twitched and contracted. Three days ago the left side of his face became weak, and weakness of the left arm muscles progressed to practically complete loss of motion. Two days ago the left leg became weak; speech gradually became difficult. For a week there has been marked photophobia. On examination after admission there were found slight cyanosis of lips, fingers, ears, and mucous membranes of mouth, and later an increased reddish color, rather than a definite cyanosis, was noted; tender point over the vertex of the head;

paralysis of the left face and arm; paresis of the left leg; hypesthesia of the left arm and leg; left astereognosis; tendency to conjugate deviation of the eyes to the right and restriction of conjugate movements to the left; deep reflexes of left arm greater than right; positive Babinski sign on left; left homonymous hemianopsia; edema and hyperemia of optic disks. His hemoglobin was 180 per cent. and red blood count 6,960,000. He had a cerebral decompression and subsequently died. Autopsy showed bilateral thrombosis of the cerebral arteries, with areas of cortical degeneration in both cerebri; mural thrombosis of the aorta; thrombosis of the coronary arteries; infarcts in the heart and spleen; splenomegaly.

Case V.—Male, aged sixty-three years, was admitted to the medical service of the Peter Bent Brigham Hospital August 16, 1915. The nervous symptoms were transitory dizzy spells for one year; toe-drop for three months; for a few months' memory had been failing; three days before admission he noticed numbness of the fingers of the left hand and increasing weakness of left arm, so by noon it was paralyzed; a little later in this day weakness began in his left leg and increased to paralysis the day of his admission. On admission there was some weakness evident on motion of the eyes to the left; paralysis of the left arm and leg with decreased reflexes; optic disks showed slight blurring. The color of the face was reddish and the lips showed a deep red-blue color. The patient remained in this general condition for two months, with a hemoglobin of 182 per cent. to 206 per cent. and red blood count of 8,944,000 to 9,320,000. He then gradually went to pieces and died. Autopsy showed thrombosis of the cerebral artery with areas of softening in the right cerebral cortex; thrombosis of the left renal, pulmonary, and splenic arteries and of the right renal vein and the inferior vena cava; infarcts of the lung and spleen; slight splenomegaly.

Case VI.—Female, aged fifty-four years, was admitted to the medical service of the Peter Bent Brigham Hospital March 20, 1916, and readmitted December 6, 1916. The nervous symptoms were dizziness of about fourteen months' duration, and for ten months occurring almost daily; for ten years she has been seeing black spots before her eyes, moving laterally (ophthalmoscopic examination shows numerous opacities in the vitreous); for some time she has had periods of feeling dazed and of other queer sensations; once while walking to the bath room it seemed as if she were trying to walk on air, and she raised her legs high like a horse; six months ago her right leg lost its power and felt dead for five minutes; she has had periods of peculiar numbness of her lips and tongue. Her color was increased and of a reddish, cyanotic type, and her hemoglobin was 164 per cent. and red blood count 7,380,000. For eight months after leaving the hospital she continued to have recurrent headache, trouble in vision, and nervousness. Then eight days

ago she had numbness of the entire right half of her body; she could move her arm and leg, but could not feel them move, though she saw that they were moving. These attacks recurred several times during the eight days, and she had difficulty in walking, staggering like a drunken man. These attacks were followed by pins and needles sensations. She has had flashes of light before her eyes and scintillating scotomata always seen to the right. On her readmission a physical examination showed slightly decreased sensations of temperature, pain, pressure, and touch on the right side of the face and right arm and leg. No signs of ataxia could be made out in the legs, but there was slight difficulty in finger-to-finger and finger-to-nose tests, apparently due to difficulty in telling where the right hand was. Her hemoglobin was 122 per cent. and red blood count 6,696,000.

CASE VII.—Male, aged fifty years, first came to the medical outdoor department of the Peter Bent Brigham Hospital August 4, 1916. The nervous symptoms were occasional headache and slight dizziness almost daily. His hemoglobin was 120 per cent. and red blood count 8,400,000. The note on his color was "looks pale in spite of high hemoglobin."

CASE VIII.—Male, aged fifty-six years, admitted to the surgical service of the Peter Bent Brigham Hospital November 22, 1916. The nervous symptoms were decreasing vision for two or three months, and for ten days slightly blurred vision and diplopia; three weeks ago he felt dizzy and staggered to the right side on several occasions; about the same time his feet began to feel numb and he would catch them on the stairs; his gait became shuffling, more on the left; for one week he was unable to walk or to move his left leg; for two weeks he had almost constant headache. On physical examination his mucous membranes were pale; there were palsy of the left arm and leg; partial paralysis of the left face; positive Babinski sign on the left; absent knee-jerks on the left. The patient gradually grew more drowsy and stuporous. On November 25 cerebral decompression was done. Subsequently blood examination showed hemoglobin of 150 per cent. and a red blood count of 9,200,000. The patient died on November 29 and autopsy showed sclerosis of the cerebral arteries and cerebral softening; the spleen was small; no thromboses of vessels were found.

CASE IX.—Male, aged fifty years, was admitted to the surgical service of the Peter Bent Brigham Hospital November 26, 1916. The nervous symptoms were slight frontal headache of three or four weeks' duration; difficulty of speech for one week, increasing in four days to inability to say more than "yes" and "no;" blurred vision for three days; paralysis of the right arm for twenty-four hours and the right leg for six hours. Physical examination showed paralysis of the left external rectus muscle of the eye; right trigeminus anesthesia; right facial paralysis; paralysis of the right

palate and right trapezius muscle; right hypoglossal paralysis; paralysis of the right arm and leg; right hemianesthesia; positive Babinski sign on right and right ankle clonus. The color does not appear to have been abnormal, as in two notes in regard to the skin no mention is made of any abnormality of color, though the blood examination showed during twelve days, three observations of hemoglobin of 137 per cent., 140 per cent., and 135 per cent., and red blood counts of 6,800,000, 6,728,000, and 7,040,000 respectively.

CASE X.—Female, aged fifty-six years, admitted to the medical service of the Peter Bent Brigham Hospital January 4, 1917, and readmitted April 21, 1917. The nervous symptoms were at first slight fulness in the head. Later there was very slight headache, numbness in one side of her face and attacks of weakness, in which, as she says, "she feels as though she was sinking down;" but these symptoms were very slight and possibly were the result of suggestion. There were no eye symptoms beyond slight fatigue and occasional blurring. The symptom that brought her to the hospital was gastric discomfort.

Her color, especially of her face and neck, was of the characteristic red cyanotic type. Blood examinations showed a variation between 128 and 155 per cent. of hemoglobin and a red blood count between 5,440,000 and 7,790,000.

Of these 10 cases which I have observed all but two (Cases II and X) showed very definite nervous symptoms, and in most the nervous disturbances were the chief cause of the patient's discomfort. These symptoms varied in duration from a few days to many years. The most frequent symptoms were headache and dizziness. Other common symptoms were disturbances of vision, such as easily induced fatigue of the eyes, blurring of vision, scotomata often scintillating, transient blindness, hemianopsia, and diplopia. Disturbances of sensation, particularly paresthesia, occurred. In several patients motor disturbances, such as paresis and paralysis, were seen. The case in which these were transient and recurred is of special interest. The nervous symptoms in some of the patients were sufficiently focal in character to lead to the diagnosis of brain tumor. Case IV was of special interest in this connection, for during a period of ten years, during which he was seen repeatedly by ophthalmologists and neurologists, brain tumor often was suggested as the cause of his symptoms, and no one seems to have suspicioned the polycythemia until he was admitted to the hospital, and even when the blood count was known it was still thought possible that some of the focal symptoms were due to a cerebral tumor.

Ascher[6] in a study of the eye changes in several patients with polycythemia notes a slight swelling of the optic disk which he thinks might be due either to the polycythemic congestion or to slight

6 Klin. Monatsbl. f. Augenh., 1914, liii, 388.

edema. He emphasizes asthenopia as a frequent symptom in patients without refractive errors. Two of our patients gave this symptom, and told of repeated but fruitless efforts to get suitable adjustment of glasses.

What is the cause of the nervous symptoms? In many of the cases undoubtedly the cause lies within the central nervous system. The contents of my consultation slip on Case IV bears on this, and I quote it in part: "The cerebral symptoms and peripheral effects might be explained as of focal origin; cerebral thromboses and hemorrhage. Both occur in reported cases. In the absence of other pressure phenomena in this case and the history of onset of paralyses I believe there is stronger probability of cerebral vascular disturbance—at first general and slight, simply disturbance in the venous channels with poor circulatory nutrition, later focal and more marked thrombotic or hemorrhagic—than of cerebral neoplasm. If the latter, it is a slowly developing type; if the former, the polycythemic condition would be the primary cause. My personal feeling is that polycythemia with secondary vascular circulatory disturbance is the probable diagnosis." In this patient and in Case V vascular thromboses were found at autopsy to explain at least the recent cerebral symptoms. These thromboses might be said to arise in part from diseased conditions in the vessel wall and in part from the changed condition of the blood. Less marked nervous symptoms on the other hand must be due to temporary circulatory disturbances, especially where they are so transitory. That more definite organic cerebral lesions may occur without evident thrombosis or lesion in the vessel wall is shown by Case VII, where with areas of cerebral softening no thrombi and almost no vascular lesion were found at autopsy. A case in every way similar to this was reported by Goldstein[7] with focal softenings in the brain and cerebral vessels free of lesions.

In this group of cases the color of the skin was very interesting. In Case I, when seen after the development of abdominal symptoms due to mesenteric thrombosis, very little cyanosis was noted, though this patient had shown the typical color during previous observations. In Case II no cyanosis or erythema was noted. In Case VII the note was made that the patient "looks pale in spite of the high hemoglobin." In Case VIII cutaneous pallor was noted and the increased hemoglobin and high blood count were not discovered until after cerebral operation. In Case IX the color does not appear to have been abnormal. In Cases III, IV, V, VI and X there was typical cyanosis or erythema. Thus of 10 cases half (5) at the time of hospital observation failed to show color in the skin that would suggest the diagnosis of polycythemia.

A striking thing in this group was the similar age at the time of

[7] Med. Klinik, 1910, vi, 1492.

administration to the hospital—51, 55, 45, 55, 63, 54, 50, 56, 50 and 55 respectively. Though this may be a mere coincidence it is rare to get so little age variation in a group of patients with a single diagnosis. From the history given by these patients it is suggested that often the blood condition exists prior to very definite symptoms of any sort and the development of symptoms may occupy a long time. We have very little data on which to base an opinion as to the probable average age of development of polycythemia. We know from observations of high blood counts among members of families of patients with polycythemia and symptoms that the condition exists without symptoms, so presumably it develops often long before symptoms occur.

SUMMARY. Nervous symptoms are very frequent in polycythemia vera, and usually they are the symptoms that lead the patient to seek medical advice. Since, quite often, polycythemic patients fail to show cyanosis or erythema, with these nervous symptoms, other cerebral lesions such as brain tumor are suspected. In the earlier stages such symptoms must result from simple circulatory disturbances; in the later stages cerebral softening or cerebral hemorrhage and local vascular lesions, such as thrombosis, are often found.

HEAT STROKE: REPORT OF ONE HUNDRED AND FIFTY-EIGHT CASES FROM COOK COUNTY HOSPITAL, CHICAGO.

By H. GAUSS, M.D.,

AND

K. A. MEYER, M.D.,

CHICAGO.

DURING July, 1916, there were admitted to the Cook County Hospital, Chicago, 158 patients suffering from sunstroke and heat exhaustion; 11 patients were admitted from July 15 to 26 and 147 from July 15 to 31. There occurred 70 deaths, making a mortality of 44.3 per cent. In the last five days of July the weather was unusually oppressive. The temperature for July was the highest of any month in forty-six years. Quoting the report of the U. S. Department of Agriculture, Weather Bureau for Chicago, "July was a record-breaking month both as regards temperature and sunshine. The monthly mean temperature was the highest on record, exceeding by 1° the previous record of 77.4° in July, 1901. The maximum temperature of 101° registered on July 30 has been exceeded only once, on July 21, 1901. From noon of July 26 to 7 A.M. of July 31 inclusive the temperature was continuously above 82°, while the highest minimum on any previous day since the records

have been kept was 81.7°." From July 26 to 30 inclusive there was 100 per cent. sunshine, the average hourly velocity of the wind for this period was 6, and the average relative humidity was 58. On July 31 there was a fall in the temperature. The mean was 82, maximum 90, minimum 75; the average hourly velocity of the wind was 16; the relative humidity was 72; the percentage of sunshine was 91.

This report is concerned with the analysis of this series of patients. The information was obtained from two sources: from the hospital histories of the patients, which include the statements of the police at the time of the admittance of each patient, and from subsequent interviews of those patients who recovered. As far as possible each patient was questioned upon his discharge, as to the onset of the disease, the prodromal symptoms, his age, nationality, occupation, the amount of alcoholic beverages consumed in the twenty-four hours previous to the attack as well as the daily average consumption, also the diet and clothing. A number of the patients were unidentified upon admittance, those who recovered were subsequently questioned; and of those who died, many were subsequently identified and the information obtained from the friends.
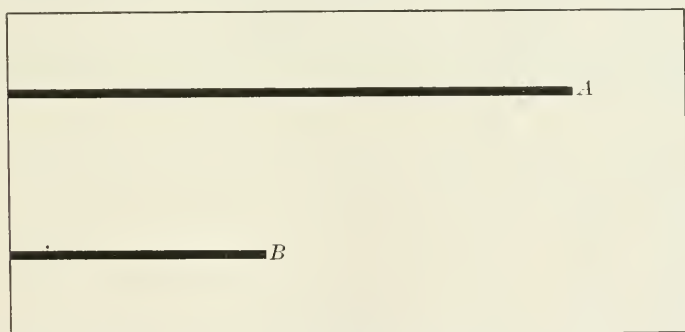
CHART I.—Mortality. A, one hundred and fifty-eight patients admitted; B, seventy deaths, or 44.3 per cent.

PREDISPOSING CAUSES. Of the 158 patients, 152, or 96.2 per cent., were males, and 6, or 3.8 per cent., were females. The ages of all but 10 were definitely established. There was one nineteen years, or 0.6 per cent. under twenty years; 13, or 8.2 per cent., from twenty to twenty-nine years; 37, or 23.4 per cent., from thirty to thirty-nine years; 41, or 26 per cent., from forty to forty-nine years; 38, or 24.1 per cent., from fifty to fifty-nine years; 13, or 8.2 per cent., from sixty to sixty-nine years; 5, or 3.2 per cent., from seventy to seventy-nine years. One hundred and sixteen patients were in the third, fourth, and fifth decades; adding to these the other 10 who are described as "about middle aged," there is 79.8 per cent. for these three decades.

As to the nationality of the patients, 45 were American-born, 103 were foreign-born, the nationality of the other 10 was not established. One of the American-born patients was a negro, who died several hours after admittance. This is interesting in view
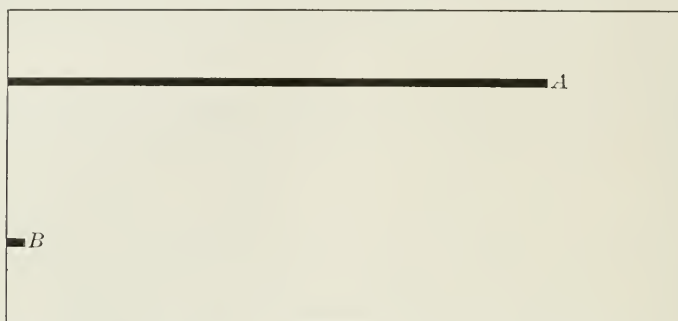
CHART II.—Sex incidence. A, one hundred and fifty-two males, or 96.2 per cent.; B, six females, or 3.8 per cent.

of the often expressed view that negroes possess a special immunity against the effects of heat. Of the foreign-born, 24 were Poles, 24 were Slavs, including the Russian group, 22 were Germans, 10 Irish, 6 Bohemians, 5 Lithuanians, 4 Englishmen, 4 Scandinavians, 4 Italians. The occupation incidence was: laborers, 85; teamsters,
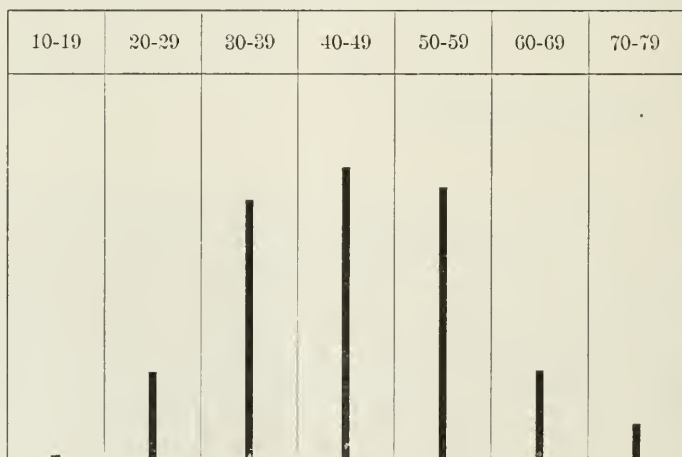
CHART III.—Age incidence.   (See text.)

12; carpenters, 8; firemen, 4; peddlers, 4; laundry workers, 3; housewives, 3; cooks, 3; clerks, 3; electrician, painter, machinist, seamstress, porter, waiter, 1 each; unknown, 27. These occupations were verified in the case of most of the patients who recovered.

The 27 not established were patients who died without regaining consciousness. The term laborer is used in a broad sense to include all untrained manual workers. Of the established occupations, laborers comprise 64.9 per cent.
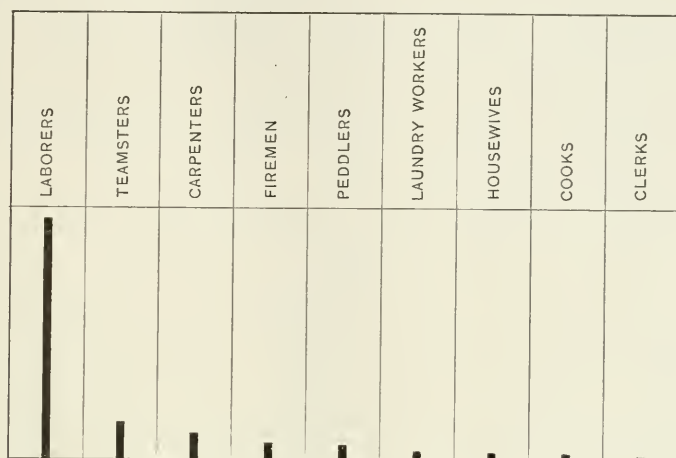
CHART IV.—Occupation incidence.   (See text.)

Most of the patients gave a history of alcoholism. Table VI gives the statements of 25 patients, with reference to the amount of
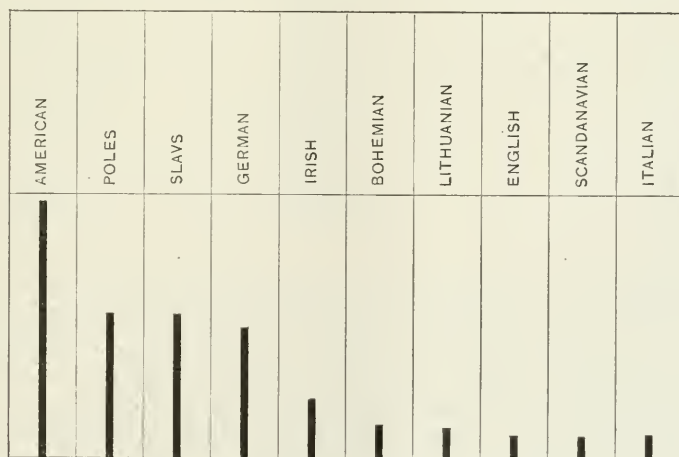
CHART V.—Nationality incidence.   (See text.)

beer consumed in the twenty-four hours previous to the attack, also the average daily consumption. In obtaining these statements no effort was made to force an answer. A number of patients also drank whisky. All but 2 of the patients drank beer in the twenty-

four hours preceding the attack, the amount varying from several
glasses to one gallon, and all but one had been in the habit of drink-
ing daily. Of those patients who did not recover consciousness
there is no definite information, but, judging from the strong alco-
holic breath of many of them, it is evident that they too had been
drinking freely. Most of the patients questioned had been in the
habit of eating meat daily. Of 25 patients, 8 ate it three times a
day, 11 twice daily, 5 once a day, and 1 did not eat it at all. As
to clothing, the majority wore thin summer cotton underwear, a
few wore woolen underwear; the outer clothing consisted of either
their regular street suits or overalls.

STATEMENT OF TWENTY-FIVE PATIENTS.   ALCOHOL AND HEAT
STROKE.

No.									Beer consumed in 24 hours before attack.	Average daily consumption.
1	.	.	.	.	.	.	.	.	1 bottle	1 to 2 glasses
2	.	.	.	.	.	.	.	.	1 gallon	5 to 10 glasses
3	.	.	.	.	.	.	.	.	2 bottles	2 to 4 bottles
4	.	.	.	.	.	.	.	.	3 glasses	2 to 4 glasses
5	.	.	.	.	.	.	.	.	6 bottles	3 to 4 glasses
6	.	.	.	.	.	.	.	.	8 bottles	2 bottles
7	.	.	.	.	.	.	.	.	4 glasses	5 to 6 glasses
8	.	.	.	.	.	.	.	.	. . . .	. . . .
9	.	.	.	.	.	.	.	.	3 pints	3 to 4 pints
10	.	.	.	.	.	.	.	.	2 glasses	3 to 5 glasses
11	.	.	.	.	.	.	.	.	1 pail	2 pails
12	.	.	.	.	.	.	.	.	1 bottle	1 to 2 bottles
13	.	.	.	.	.	.	.	.	1 pint	1 pint
14	.	.	.	.	.	.	.	.	1 pint	1 pint
15	.	.	.	.	.	.	.	.	3 bottles	3 to 4 bottles
16	.	.	.	.	.	.	.	.	5 bottles	3 to 4 glasses
17	.	.	.	.	.	.	.	.	3 pints	3 to 4 pints
18	.	.	.	.	.	.	.	.	3 pints	2 to 3 pints
19	.	.	.	.	.	.	.	.	6 glasses	2 to 3 pints
20	.	.	.	.	.	.	.	.	1 bottle	1 bottle
21	.	.	.	.	.	.	.	.	4 glasses	3 to 4 glasses
22	.	.	.	.	.	.	.	.	2 bottles	1 pint
23	.	.	.	.	.	.	.	.	3 glasses	4 glasses
24	.	.	.	.	.	.	.	.	5 to 6 glasses	15 to 20 glasses
25	.	.	.	.	.	.	.		. . . .	2 to 4 glasses

PATHOLOGY. Postmortem examinations were performed by Dr.
E. R. Le Count. The following anatomical alterations were found:
edema of the leptomeninges, brain, and lungs; cloudy swelling of
the myocardium, liver, and kidneys; fatty changes in the liver;
petechial hemorrhages in the brain, viscera, and skin.

SYMPTOMATOLOGY. The period of prodromal symptoms was
found to vary from five days to a few seconds. The patients com-
plained of headache, dizziness, malaise, anorexia, polydipsia,
nausea, vomiting, diarrhea, epigastric distress, restlessness, stupor,
insomnia, dyspnea. Headache and dizziness were commonest, and
occurred in most of the patients. It was observed that in many
patients in whom the prodromal period was a day or more the

temperature on admittance was not high; where the period of pro-
dromal symptoms was a few hours or less the temperature was
high. This was not always true; the reverse was also noted, but
less frequently. In a number of patients the attack came on instan-
taneously. One teamster left his wagon to get a drink of water;
he felt perfectly well when he left his seat; as he stooped to drink
from the fountain, he felt himself slipping, and remembered nothing
further until he awoke in the hospital. He had a temperature of
110° on admittance. A laborer who also had a temperature of
110° stated that he was cleaning street cars at a terminal barn,
and that he was just leaving one car to enter another when he lost
consciousness. He insisted that he knew nothing after leaving the
car, and that he felt perfectly well up to that moment, and had no
unpleasant sensations then. A number of patients who had severe
headaches and who were dizzy went walking in effort to find relief,
and dropped in the streets; many were lying in bed when they lost
consciousness. The nature of the place the patients were found was
specifically stated in the police reports of 121 patients; 40 were
found in the streets; 49 were brought from private homes; 18 were
brought from lodging houses; 14 were found at places where they
were working; 5 patients walked to the hospital; 1 of these had a
temperature of 104.8°.

The temperature on admittance varied from 94° to 114°. In
recording the temperatures the usual clinical thermometers were
used. In a number of patients the mercury was forced to the upper
end of the thermometer. These thermometers are calibrated up
to 110°, but the space above the 110° mark, calibrated on the same
scale, is equivalent to 4°. It is probable that if suitable thermom-
eters had been on hand even greater temperatures would have
been recorded. A laboratory thermometer was used on a few
patients; temperatures of 113° were recorded; but these thermom-
eters are not self-retaining, and the mercury fell rapidly when the
thermometer was removed from the body; so these do not represent
the maximum temperatures. In this paper all temperatures above
110° will be grouped with 110°. Heat cases are usually classified
into heat exhaustion and sunstroke according to the temperature
of the patient. The former are described as having subnormal to
normal temperatures, and the latter very high temperatures. In
this series there is no strict line of separation. All temperatures
between the two extremes mentioned were found. The admit-
tance temperatures and number of deaths occurring in each were
as follows: 1 patient was admitted with a temperature of 94°, he
recovered; 2 patients had 97°, they recovered; 8 patients had 98°,
3 of them died; 15 patients had 99°, 2 died; 6 patients had 100°
and 2 died; there were 12 with 101° and 3 deaths; 5 with 102° and
2 deaths; 5 with 103° and 2 deaths; 7 with 104° and 3 deaths; 9
with 105° and 3 deaths; 7 with 106° and 3 deaths; 16 with 107°

and 4 deaths; 6 with 108° and 3 deaths; 19 with 109° and 5 deaths; 38 with 110° and 31 deaths. Four patients died before their temperatures could be recorded. The temperature curves presented a
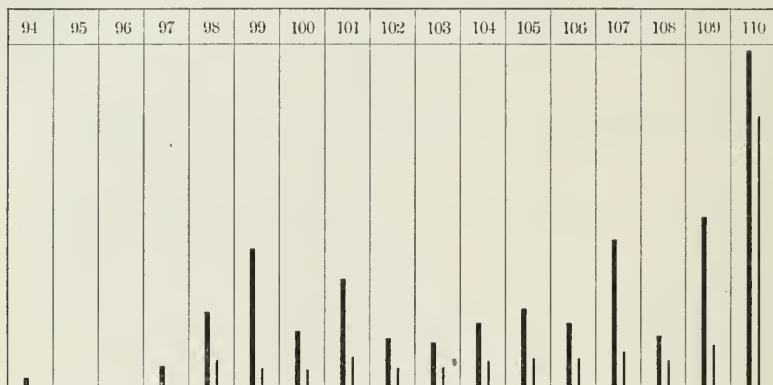
CHART VI.—Admittance, temperature, and deaths. The heavy lines indicate the number of patients, the light lines the number of deaths in each group. (See text.)
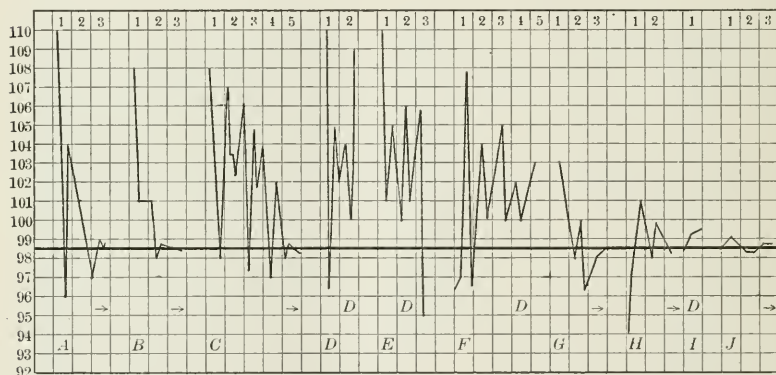
CHART VII.—Temperature curve types. A, high temperature with drop of 14° in one-half hour, patient recovered; B, high temperature with slower progressive drop and no recurrences, patient recovered; C, high temperature with several recurrences, patient recovered (note the periodicity); D, high temperature with death occurring on an ascending temperature; E, high temperature with death occurring on a falling temperature; F, subnormal temperature with marked rise in several hours, patient died; G, intermediate type of temperature, patient recovered; H, marked subnormal temperature with recovery; I, normal temperature followed by death; J, normal temperature followed by recovery. All of these patients were comatose upon admittance.

great number of variations. Following the hydrotherapeutic measures to which the hyperpyrexial patients were subjected, there was a sudden fall in the temperatures, varying from 2° to 14°, and subnormal temperatures being reached frequently. In some

patients there was a slower but progressive fall until normal was reached, which was then usually maintained; in others there were recurrences of 1° to 9°, and 1 to 5 in number. The time that it required the hyperpyrexial patients to return to normal varied from ten minutes to three days. When the return to normal was less than several hours, recurrences usually took place. The terminal temperatures varied from 95° to 110°. A few patient admitted with subnormal temperatures had a rise of 5° to 9° within a few hours.

The pulse-rates on admittance were roughly proportional to the temperatures. Patients with temperatures up to 99° had pulse-rates from 70 to 104; in patients with temperatures from 100° to 102° the pulse-rates were 80 to 134; patients with temperatures from 103° to 107° had pulse-rates from 112 to 152; patients with temperatures above 108° had pulse-rates from 148 to 180. The pulse-rates usually fell with the temperature and rose with it. Comatose patients with high temperatures usually had an easily compressible, rapid, weak peripheral pulse. The quality of the pulse usually improved with the fall in temperature, and became weak, irregular, and imperceptible if the coma deepened or the temperature rose.

The respiration of comatose patients was usually labored, rapid, shallow, and gasping. Many patients uttered a respiratory grunt or moan with each inspiration. Coarse mucous rales were heard in large number, and a tracheal rattle in the fatally ending cases. The respiratory rates varied from 16 to 48 in patients with temperatures up to 105° and from 30 to 60 above 105°. The respiratory rates usually returned to normal with the temperature. In many patients a peculiar fetid odor was noted to the breath in addition to the alcoholic odor.

Ten patients injured themselves and sustained slight abrasions of the skin, scalp, tongue, or lips. The skin was commonly hot, dry, and cyanotic, and after a decrease in temperature cold and clammy. Nearly all of the patients had involuntary bowel movements. Many vomited and a few had hemorrhages per rectum and bloody vomitus. After the return of consciousness the appetite was poor and a few had difficulty in swallowing.

The urine of 25 patients was examined on their second day in the ward. In all, large numbers of hyaline and granular casts were found; in all but 5 pus cells were found. Albumin, as determined by the nitric acid ring test, was observed in 5, and sugar in 1. The specific gravity average for the 25 was 1.020. The systolic blood-pressure was taken on these same patients. Four were between 90 and 100, 3 between 101 and 110, 4 from 111 to 120, 9 from 121 to 130, 2 from 131 to 140, and 1 each in the three next 10 mms. White cell counts also made on these patients varied from 7200 to 20,200. There were 3 under 10,000, 13 from 10,000 to 15,000,

and 9 above 15,000. Differential cell counts were within the limits of normal in 18, and in 7 there was an increase in the percentage of lymphocytes.

One hundred twenty-nine patients were in coma on admittance, 10 were stuporous but could be aroused, 3 were in active delirium, and 16 were conscious and rational. Fifty-eight died without regaining consciousness and 10 had relapses after regaining consciousness and died; the other two deaths occurred in patients who were conscious on admittance. The reflexes varied with the depth of the coma. In the deep comatose condition all the reflexes were abolished, even the corneal in several instances, in the semicomatose condition, the superficial reflexes were absent, and in the conscious patient all the reflexes had returned. Most of the patients manifested some form of symptoms resulting from cerebrospinal excitation. Thirty-six patients had generalized convulsions of either the tonic or clonic type, and in a few patients both forms occurred. Clonic convulsions lasted from one to ten minutes and occurred from one to six in number; the tonic convulsions lasted from one to five minutes. Focal tonic and clonic convulsions occurred in 24 patients; the parts of the body involved were the extremities, lower or upper, or frequently a single limb, also the neck and muscles of the face. In the convulsive attack as well as in the mental symptoms, a resemblance was noted in many instances to the epileptic attack. Two patients uttered a shrill cry immediately preceding the convulsions. Thirty-four patients had a form of general restlessness associated with incoherent muttering or active delirium. Only 54 patients did not manifest some form of these symptoms according to the records, and this figure is probably too high. In the great stress that the hospital staff was suddenly called upon by this emergency it is probable that many symptoms went unrecorded, the best efforts of the staff being directed to the patients themselves; the fact that many of the records are complete even to details speaks well for the resident and nursing staffs. Upon emerging from coma a number of patients had marked disturbance of speech. Although they appeared to be rational and could consistently answer questions which required an affirmative or negative shake of the head, their spoken answers were inarticulate, guttural, meaningless sounds; a few would not attempt to speak at all; others manifested a form of ill humor commonly met in epileptic patients following an attack, in which the patient's attention can be attracted but not held, and questioning seems to irritate them. In other patients orientation was lost. Orientation as to person returned first, then to place, and lastly but somewhat delayed to time. A few patients seemed to have delusions and hallucinations; thus one patient was afraid that his wife and daughter were trying to kill him, and another asked who was constantly calling his name. Consciousness generally returned

in three to ten hours, and was followed by a deep sleep. In a few instances consciousness returned within a half hour or was delayed to twenty-four to seventy-two hours. An instance of a favorable result was a laborer found unconscious in the street and admitted to the ward in coma with a temperature of 109.2°. He was given a cold water friction bath for fifteen minutes and returned to the ward with a temperature of 100.4°. Fifteen minutes later he was conscious and complained of a slight headache; he fell asleep and awoke several hours later, when he felt well and had a normal temperature. He left the hospital the following day apparently well. An instance of an unfavorable result was another laborer, also found unconscious on the streets, and on admittance, July 26, 10 A.M., had a temperature of 104°. After a similar bath he had a temperature of 102°; he was very restless and talked irrationally; his restlessness continued to the evening and his temperature rose to 104°; his face was flushed and he perspired profusely. July 27 he seemed improved, his restlessness subsided, and he appeared to be rational; he called for water but was unable to swallow it; his temperature was 103°. At 6 A.M. he was observed to have a clonic convulsion of the extremities, lasting a few minutes. At 8 A.M. he again appeared rational, was able to swallow water, and responded well to questions; his temperature was 101°; in the afternoon he appeared stuporous, his temperature was 103°. July 28, at 1 A.M., he had a general clonic convulsion lasting two minutes, following a short tonic spasm of the extremities; he foamed at the mouth and his eyes were blank and staring; following the attack he broke out into a profuse sweat; he remained stuporous until 1 P.M., when he had a similar convulsion, but during the tonic spasm of which his neck became rigid, his head was drawn back, and his face distorted, his temperature was 105°. He remained in a stuporous condition the remainder of the day. July 29 the patient was still stuporous; he was perspiring profusely and his temperature had risen to 109°. Following a cold bath he had another general convulsion and his temperature fell to 96.8°. At noon he was again irrational, very cyanotic; his temperature rose to 105.6°; at 2 P.M. he had another general convulsion; death occurred at 3 P.M.

TREATMENT. All patients with a temperature of 103° or over were immediately placed in a tub of tap water, the level of which was just high enough to cover the body except the head, which was supported in a hammock packed with ice. Vigorous friction was applied to the entire body by four or more persons; ice was freely added to the water, the friction being constantly maintained; the temperature was taken rectally every minute. When the temperature reached 102° the patient was removed from the bath, wrapped in sheets or blankets, and returned to the ward. Generally 102° was reached in ten to thirty minutes. When the patients were returned to the wards their temperature usually continued to fall

frequently, reaching subnormal 95° to 97°. Cardiac stimulants were given freely, strychnin, sodium caffein benzoate, digitalis, strophanthus; an ice-bag was placed at the head and chipped ice was given by mouth. For subnormal temperature external heat was applied. For recurrences in temperatures up to 103° cold packs and alcohol sponges were given; above 103° the patient was again given a cold water friction bath. It was observed that recurrent temperatures could not be reduced as easily as the initial high temperature, and in a few instances the temperature continued to rise in spite of prolonged friction in cold water. For restlessness and convulsions sedatives were used; morphin, chloral hydrate, scopolomin, the bromids, and mechanical restraints.

AN ELECTROCARDIOGRAPHIC STUDY OF A HEART SHOWING ECTOPIC AURICULAR CONTRACTIONS, WITH SPECIAL REFERENCE TO THE INFLUENCE OF THE VAGUS NERVES ON THE ECTOPIC FOCUS.

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That the vagus nerves influence the rhythmicity, contractility, conductivity, and irritability of the heart is well known, but it seems probable that the two nerves do not exercise the same influence over the various cardiac properties, at least not in the same degree. The idea is gaining ground that the specialized tissues are more richly supplied with vagus fibers than the main mass of cardiac muscle, and that it is to the distribution of the two nerves that their specific action is due. There is evidence for the belief that the specialized tissue in the region of highest rhythmicity—that is, the right auricular sinus—is supplied mainly by the right vagus; while the specialized tissue between the auricles and ventricles that conducts the impulse downward, receives its nerve supply mainly from the left vagus. The latter, therefore, exercises a greater influence over conduction, just as the right vagus has the greater control over the heart rate. The extent to which the vagi supply the undifferentiated portions of the heart muscle is not so well understood. Cases showing vagus influence on ectopic beats are very rare. Whether this is because such beats usually arise outside the specialized tissues cannot be decided at present. The case forming the basis of this paper shows a vagus influence upon the occurrence of beats that arise in an ectopic focus of stimulus production, and is thought worthy of record for that reason. It is

also an example of an unusual type of constant arrhythmia, and it shows how a study of the time relationship between a premature auricular contraction and the normal ventricular systole may be important in determining the cause underlying the varying effect of the ectopic beats upon ventricular activity. It records, furthermore, a change in the form of the normal auricular complex apparently due to vagus influence.

The patient whose electrocardiographic records have been studied exhibited cardiac arrhythmia a year or more before his admission to the Barnes Hospital, during an examination for insurance, at which time it was observed that his pulse was bigeminal. The illness for which he was admitted to the hospital, diagnosed influenza, apparently therefore had no relation to his cardiac abnormality. He had gonorrhea three years before his admission. There is no history of other infectious disease. He had had some dizziness, weakness, and palpitation of the heart for several years, and is of the type commonly called "neurotic." At no time has there been any evidence of impairment of the functional efficiency of the heart, nor has physical examination revealed signs of an organic lesion.

Electrocardiograms have been obtained at intervals over a period of ten months. Throughout all of the records an abnormal auricular wave occurs at varying intervals. In lead I this is seen as a small notch on the terminal portion of the ventricular complex of the preceding beat, and in leads II and III it has the form of a downwardly deflected wave in the same position (Fig. 1). This abnormal wave, designated P' in the records, is followed at times by a normal ventricular complex; at times it occurs alone, and at other times an abnormal or aberrant complex follows it.

The auricular contraction then which the abnormal wave represents arises in some abnormal focus of stimulus production and occurs prematurely, the contraction taking place before the preceding normal systole of the ventricles is complete. At times this premature auricular[1] contraction sets up a normal contraction of the ventricles, at times it causes no ventricular response, and at other times the response of the ventricles is abnormal or aberrant. It was to seek the explanation of these phenomena, as well as the explanation of the irregular occurrence of the ectopic beat, that this study was undertaken.

It was found that the ectopic focus of stimulus production was under the control of the vagi and the extent and character of this control were studied in numerous electrocardiograms. Curves were made also so as to record the effect of paralysis of the vagus terminations by subcutaneous injections of atropin, to show the

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[1] The ectopic beats are referred to as auricular beats: whether indeed the focus whence they arise is in the lower zone of the auricle or in the higher levels of the junctional tissues is perhaps a matter of some question.

effect of exercise and of stimulation of the vagi by pressure over the nerves in the neck.

The patient was given $\frac{1}{30}$ grain of atropin subcutaneously on several occasions, and the resulting behavior of the heart, as recorded in the electrocardiograms, was always the same. The rate was slowed at first, due to the well-known stimulating effect of atropin
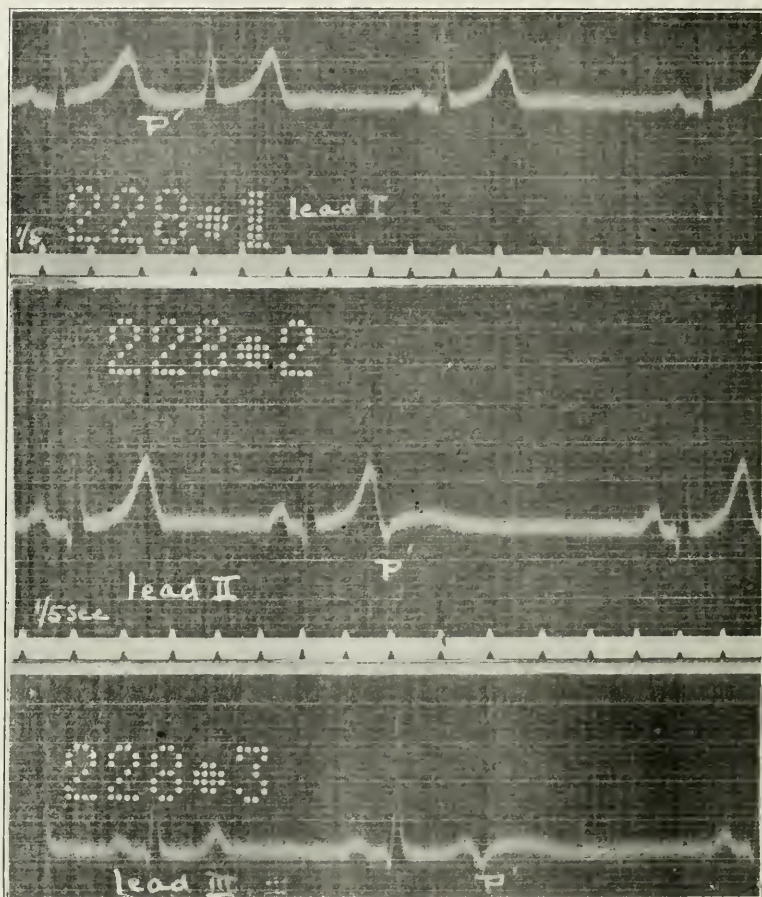
FIG. 1.—Electrocardiograms showing the abnormal P wave in all three leads.

on the vagus terminations soon after injection. The ectopic auricular contractions did not occur during this period of vagus stimulation, but as the rate began to increase the ectopic beats became more and more frequent, and finally they occurred regularly at one-third the rate of the pace-maker.

These and other details of the effects of atropin on the heart
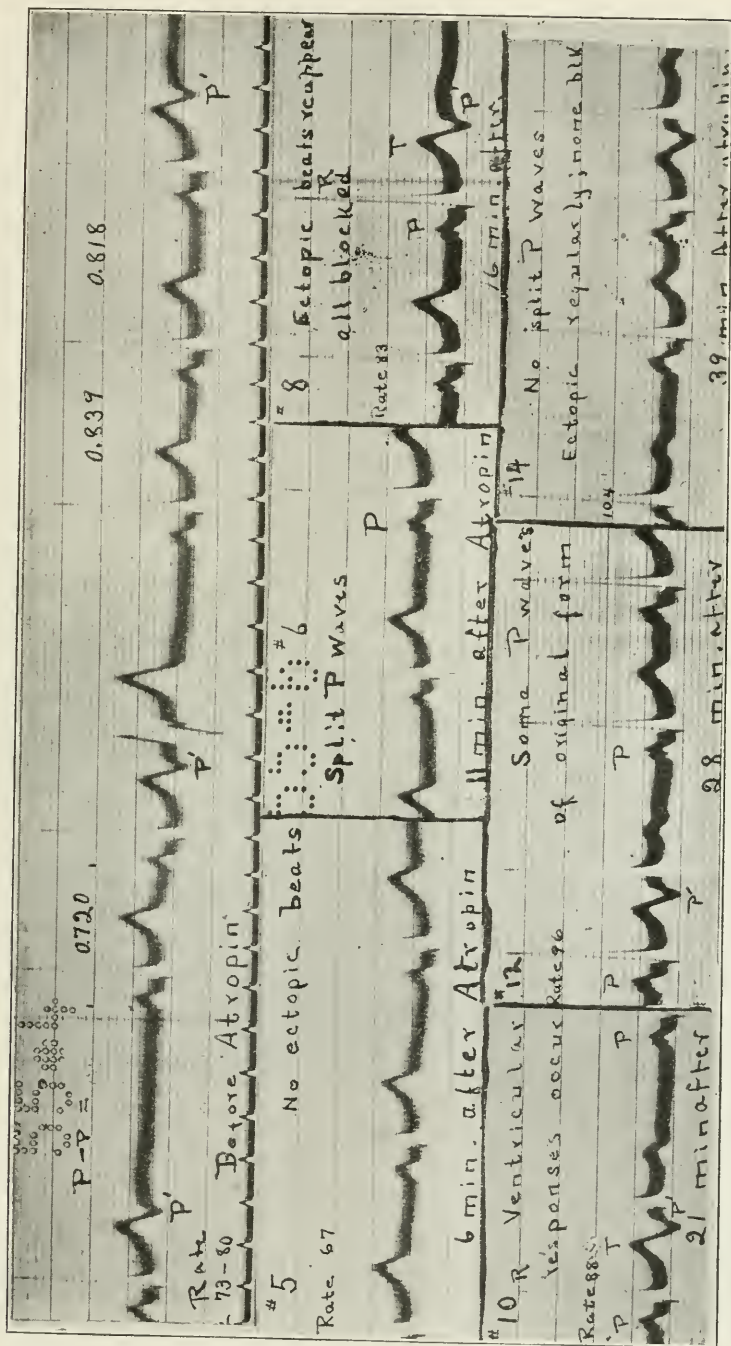
FIG. 2.—Electrocardiograms obtained during the first atropin experiment. The record obtained before atropin injection shows an aberrant ventricular complex following a negative P wave. Records were numbered in order and some are not reproduced. (See Table I.)

during two experiments are given in tabular form, the phenomena that show the effects on the auricular activity being shown in the first column; the time and accompanying effects during each experiment, in the other columns. The results of two experiments are recorded. In the first column under each experiment is given the time elapsing between the injection of atropin and the recording of the auricular phenomenon mentioned in the large column at the left of the table. The records were taken at intervals of from two to five minutes, and show, therefore, only approximately the time after atropin at which the various phenomena appeared. The figures in the second small column refer to the numbers of the curves taken during the experiment. In the third column is recorded the rate per minute as estimated from the average interauricular interval. The fourth column gives the auriculoventricular conduction time. The fifth column gives the time elapsing between the onset of the normal ventricular systole and the occurrence of the ectopic beat of the auricles. Since the beginning of the P' wave cannot be determined because of its blending with the preceding T wave, a constant point on the P' wave is used for the measurements. The point selected is the near point of the lowest part of the P' wave, and the figures given are therefore not a measure of the true $R–P'$ time, but serve just as well for comparative observations. The sixth column measures the duration of ventricular systole. (Here again the figures are not absolute, the crest of the T wave being selected as a constant point.) The last column gives the $P'–Q'$ time. (This is measured from the beginning of the horizontal portion following the P' wave, and to this is added in the earlier curves the length of the P' wave as measured in the later curves.)

TABLE I.—EXPERIMENT 55. BEFORE ATROPIN. ECTOPIC BEAT AFTER EVERY TWO OR THREE NORMAL BEATS. NEARLY ALL BLOCKED.

Effect of atropin gr. 1/30 hypo- on auricular activity.	Time after injection.	Curve No.	Rate per minute.	Conduction, average P-Q time seconds.	Average R-P'time seconds.	Average R-T time seconds.	Average P'-Q' time.
	Before 6 min.	4	73–80	0.161	0.355	0.295	0.216
Ectopic beats disappear . .		5	67	0.164			
Slowest rate	11 "	6	66	0.154	....	0.286	
Appearance of "split" P waves	11 "	6					
Ectopic beats reappear— blocked	16 "	8	83	0.144	0.348	0.292	
Ectopic beats continue, all blocked	18 "	9	79	0.141	0.340	0.289	
Some ectopic beats followed by ventricular response .	21 "	10	88	0.141	0.369	0.281	0.190
Some P waves of original form appear	28 "	12	96	0.147			
Disappearance of "split" P waves	39 "	14	104	0.146			
Ectopic beats appear regularly after every 2 normal beats. None blocked . .	39 "	14	104	0.146	0.341	0.250	0.179
Fastest rate	56 "	17	108	0.148	0.356	0.243	
Last record after atropin . .	56 "	17	....	....	....	....	0.178

TABLE 11.—EXPERIMENT 228. BEFORE ATROPIN. ECTOPIC BEAT AFTER EVERY TWO TO SIX NORMAL BEATS. VERY FEW BLOCKED.

Effect of atropin-gr. 1/30 hypo- on auricular activity.	Time after injection.	Curve No.	Rate per minute.	Conduction, average P-Q time seconds.	Average R-P'time seconds.	Average R-T time seconds.	Average P'-Q' time.
	Before	2	56–65	0.155	0.360	0.290	0.294
Ectopic beats disappear . .	9 min.	11	56	0.149			
Slowest rate	9 "	11	56	0.149	. . . .	0.295	
Appearance of "split" P waves	9 "	11					
Ectopic beats reappear— blocked	10½ "	12	70	0.151	0.359	0.294	
Ectopic beats continue, all blocked	14 "	13	75	0.150	0.359	0.292	
Some ectopic beats followed by ventricular response .	16½ "	14	78	0.150	0.356	0.284	0.201
Some P waves of original form appear	28 "	17	92	0.159			
Disappearance of "split" P waves	28 "	17	92	0.159			
Ectopic beats appear regularly after every 2 normal beats. None blocked. . .	28 "	17	92	0.159	0.372	0.250	0.179
Fastest rate	48½ "	20	101	0.164	0.397	0.235	0.149
Last record after atropin . .	60 "	23	101	0.156	0.401	. . . .	0.133

In the first atropin experiment (experiment 55, Table 1; Fig. 2), before the injection the normal auricular rate was 73 to 80 per minute, and the ectopic auricular beats were occurring, in their usual position, after every two or three normal beats of the auricles. Very few of the ectopic beats were followed by a contraction
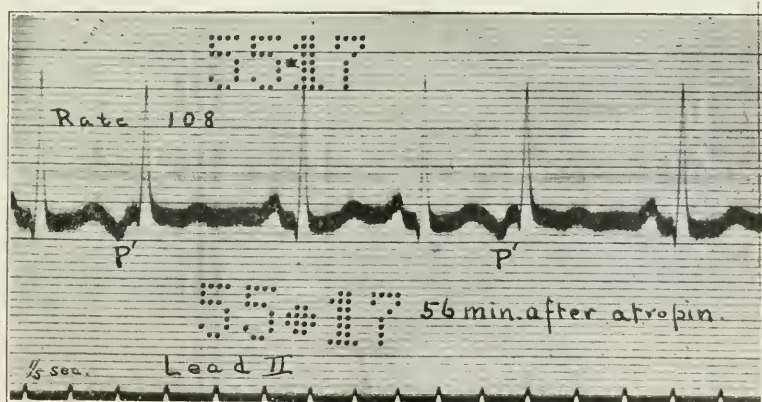
FIG. 3.—Electrocardiogram obtained during the first atropin experiment at the height of vagus paralysis. Negative P waves occur regularly and frequently, and all are followed by ventricular complexes.

of the ventricles. Soon after the injection of atropin a moderate slowing of the heart-rate occurred, as is generally observed, due apparently to a stage of vagus stimulation which precedes paralysis. During this period of slowing, at about six minutes after injection, the ectopic beats disappeared, and a little later the form of the normal auricular complex changed, becoming bifurcated. At

sixteen minutes after the injection the stage of vagus paralysis had begun, as indicated by an increase in the rate to 83 per minute. At this time some of the ectopic auricular beats reappeared, occurring at irregular intervals, but none were followed by a response of the ventricles. At twenty-one minutes some ectopic beats began to stimulate ventricular contractions, and at thirty-nine minutes, when paralysis was so far complete as to cause a rate of 104, an ectopic auricular beat was occurring regularly after every second normal auricular beat, and each was followed by a response of the ventricles. This continued, with further increase in rate, to the end of the experiment (Fig. 3).
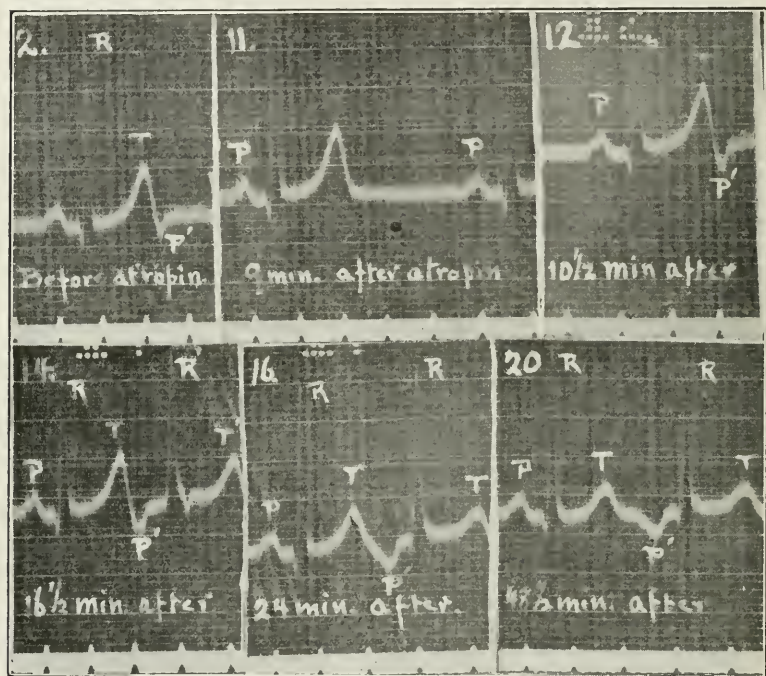
Fig. 4.—Electrocardiograms obtained during the second atropin experiment. Figures on the records refer to the table. Ventricular responses occur in Nos. 14 to 16, when the R-T time begins to shorten, though there is, as yet, no increase in R-P' time.

In the second atropin experiment (experiment 228, Table II; Fig. 4) before the injection the ectopic beats were occurring less frequently than in the first experiment, and almost all were followed by ventricular contractions. Notwithstanding this difference in the relative frequency of the ectopic beats, and the greater frequency with which they were stimulating the ventricles to a contraction, their behavior under atropin paralysis was practically
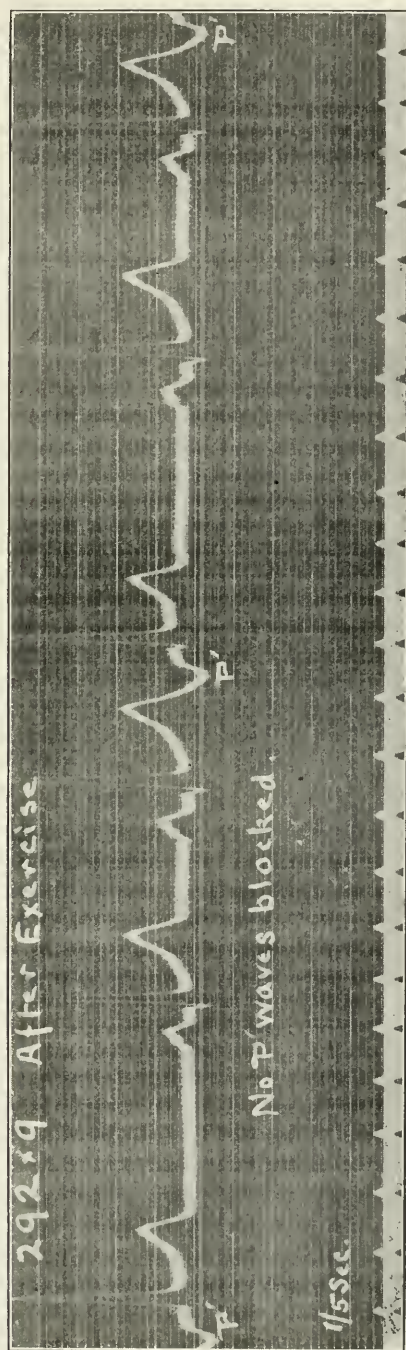
Fig. 5.—After exercise. Rate 75. Negative *P* waves occur regularly after every second normal auricular complex. All are followed by ventricular complexes.

identical with that in experiment 55. In the early period of vagus stimulation they disappeared; with the increase in rate as vagus paralysis began to manifest itself they reappeared at intervals, without stimulating at this time contractions of the ventricles. And later, under more complete atropin effect, they occurred regularly after every second normal beat, all at this period causing ventricular responses. It is worthy of mention that with the increase in vagus paralysis the "split" form of the normal auricular wave began to disappear, and finally at the time of the regular occurrence of the ectopic beats, when vagus paralysis was quite extensive, the normal form of the auricular wave was the only one occurring.

Besides the usual acceleration, three features then are worthy of comment in discussing the effect of atropin on the heart-beat of this patient: (1) the changes in the frequency of the ectopic auricular contractions; (2) the varying manner in which these impulses affect ventricular activity; (3) the alteration in the form of the complex yielded by the normal auricular contractions.

It was observed that the effect of atropin on the occurrence of the ectopic auricular beats was the same in the two experiments, though their relative frequency differed before the administration of atropin. For the first few minutes, during vagus stimulation, the normal pace-maker was depressed and the rate was slowed. This stimulation of the vagus was active at the ectopic focus also and the abnormal waves disappeared. As the stimulation began to give way to vagus paralysis the normal beats increased in frequency and the abnormal contractions also began to appear. Both increased in frequency until the vagus terminations were completely under the influence of the atropin, at which time the normal rate had been increased thirty-five or forty beats per minute, and the ectopic focus was initiating regularly every third auricular contraction. It appears, therefore, that the vagi influence the rate of stimulus formation at the ectopic focus as well as the rate of stimulus formation in the normal pace-maker. When the latter is slowed by vagus stimulation the ectopic focus also is depressed and fails to generate impulses; and when the pace-maker is freed of vagus control and the normal rate increases, the ectopic focus also initiates contractions regularly at as high a rate as 36 per minute.

The manner in which the ectopic impulses affect ventricular activity also is subject to the same variations in the two experiments, as was pointed out above. During the time of vagus stimulation the ectopic beats do not occur, and a little later, when vagus paralysis is increasing, as indicated by the increase in rate, these beats appear; but at this time none of them stimulate the ventricles to respond. Later, with the increase in rate, occasional responses of the ventricles occur, and still later all of the regularly occurring ectopic beats are followed by contractions of the ventricles.

The cause of this variation in the manner in which the ectopic beat affects ventricular activity is not easy to determine. In seeking an explanation of this phenomenon several questions arise for consideration: Is the path of the ectopic impulse to the ventricles the seat of some conduction defect? Does the premature beat, at the period when no ventricular responses follow it, occur so closely following the normal beat of the auricles that the bundle has not had time to recover sufficiently by the time the premature beat reaches it to conduct the ectopic impulse to the ventricles? Does atropin improve conduction in the path taken by the ectopic impulse to such an extent as to overcome any such hindrance as may be present? Does the ectopic impulse upon its arrival at the ventricles find the latter still refractory from the normal contraction that has just occurred, and on this account, unable to beat again in response to the ectopic impulse?

An extended discussion of these various possible factors and the part each may play in the behavior of the ventricles following the ectopic impulse would lead too far afield. It may be pointed out, however, that the conduction time of the abnormal impulse, the P'-Q' time, decreases under atropin, as shown in the tables. On the other hand, strips of a long record when no atropin has been administered may show many ectopic beats accompanied by ventricular responses and many others that cause no response of the ventricles. There is no constant relationship in records taken under atropin or in those without atropin, between the time relationship of the premature beat to the preceding ventricular systole. This R-P' time varies slightly, but in no constant way as related to the presence or absence of ventricular complexes. A study of the tables shows that ventricular responses occur at those times when the period of ventricular systole, as estimated by the R-T time, is short. This occurs with increase in rate, and may be the chief factor in allowing a response of the ventricles to the ectopic beat. With a shorter ventricular systole the refractory phase of the ventricles passes off more quickly, and an impulse from above, though reaching them in the same absolute time interval, would find the ventricles in a later phase and sooner ready to contract again. A careful study of many records shows that the failure of the ventricles to respond to the ectopic auricular beat always occurs with a change to a slower rate; and with the slower rate, ventricular systole is, of course, prolonged. When the rate is fast, following atropin administration, exercise or sinus arrhythmia, the premature beats succeed in stimulating the ventricles to respond.

Whether any one factor can be regarded as the only or indeed as the chief influence in producing ventricular responses to the ectopic beats is perhaps an open question. Whatever the cause, however, the same influences probably operate to produce the aberrant complexes. These occur both under atropin and in

curves when no atropin has been administered, when the rate is intermediate between that rate at which no responses of the ventricles follow the premature beats· and the rate at which all premature beats produce responses of the ventricles that are of approximately normal form. At these times apparently a ventricular contraction occurs before the refractory phase has passed off entirely or before the *a-v* bundle has recovered, as the case may be, and contractions yielding abnormal or aberrant ventricular complexes take place. According to Robinson[2] the abnormal form of the *Q, R, S,* group of the ventricular complex is caused by incomplete recovery of the intraventricular conducting system. He believes that the impulse reaches the ventricles when the intraventricular conducting system is in a state of functional fatigue, so that the passage of the impulse through the ventricles does not take place in a normal manner.

The point to be emphasized in considering the influence that the injection of atropin had on the relation of the ectopic auricular impulses to ventricular activity is the fact that certain factors other than a change in conduction may be important in causing the failure of the ventricles to respond to the ectopic impulse. The time relationship of the ectopic auricular impulse to the refractory phase of the ventricles must always be borne in mind when considering the failure of premature impulses to cause ventricular response, and the production of aberrant ventricular complexes. This time relationship may be modified by the earlier or later occurrence of the ectopic beat as has been pointed out by Lewis[3] or the determining factor may be a change in the duration of ventricular systole.

The electrocardiograms obtained following the administration of atropin show a change in the form of the waves yielded by the normal auricular contractions. This change consists of a splitting of the *P* wave, which appears during the period of vagus stimulation and passes off when vagus paralysis becomes established: Changes similar to these have been discussed by Meek and Eyster[4] and by Weil,[5] who consider that the alteration in the form indicates a depression in sino-auricular conduction, and regard the split waves as a record of sinus and auricular activity separated from one another. The possibility that this splitting indicates a displacement of the point of origin of the impulse must also be con-

[2] Arch. Int. Med., 1916, xviii, 830, The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart.

[3] Heart, 1910, ii, 23, Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Ventricular Musculature. Heart, 1912, iii, 279. Observations upon Disorders of the Heart Action.

[4] Am. Jour. Physiol., 1914, xxxiv, 368, Experiments on the Origin and Propagation of the Impulse in the Heart, etc.

[5] Deutsch. Arch. f. klin. Med., 1914, cxvi, 486, Beiträge zur klinischen Elektrokardiographie.

sidered. The significance of the splitting of the P wave under the influence of atropin will not be discussed further at this time.

It has been seen that when the rate of the pace-maker is slow during vagus stimulation in the early phase of atropin action, the ectopic focus also is depressed and the premature beats do not occur; and when the normal rate later is increased with atropin paralysis the ectopic beats also occur more frequently and quite regularly. The same phenomenon is observed accompanying an increase in rate with exercise. A record obtained before exercise shows the pace-maker initiating normal auricular contractions at the rate of 58 per minute, and an ectopic contraction occurring after every third normal beat. After exercise (Fig. 5) the rate of the normal auricular impulses had increased to 75 per minute and the rate of the ectopic beats also had increased so that one of these occurred after every second normal beat. During this period of increased rate all the ectopic beats were followed by ventricular responses, while before exercise, with the slower rate, very few were stimulating the ventricles to respond.

Stimulation of the vagi by pressure over the carotid artery, either on the right or left side of the neck, was done on several occasions. The heart-rate was usually moderately slowed by pressure on either side. On two occasions, once with right and once with left vagus pressure, the ectopic beats disappeared with a coincident slowing of the auricular rate. Although this phenomenon was not constant its occurrence strengthens the belief gained from the atropin experiments that the rate of ectopic stimulus formation was under the control of the vagi as well as the rate of stimulus formation in the normal pace-maker. This belief is still further strengthened by observing the behavior of the ectopic focus accompanying changes in vagus tone as indicated by sinus arrhythmia. Wherever changes in the relative frequency of the ectopic beats occur, parallel changes in vagus tone at the sinus are indicated by a change in the rate of the normal auricular beats.

On one occasion pressure over the right vagus caused a prolonged cessation of impulse formation in the normal pace-maker, and allowed some other point in the auricles to initiate contractions which yielded negative P waves (Fig. 6). The form of these negative waves differs somewhat from that of the usual ectopic beats,[6] which makes it seem probable that the impulse to the contractions which produced the two waves was initiated at some new focus. The occurrence of the next ectopic beat of usual type sequentially and so closely after the second negative wave in question strengthens this belief. The following ectopic beat of usual type (P') occurs after only one normal auricular beat, the sequence having been

[6] The form of these waves unmodified by the preceding T wave can be seen in the latter part of Fig. 4.

Fig. 6.—Electrocardiogram obtained during right vagus pressure. In two instances the normal auricular complexes are replaced by abnormal waves.
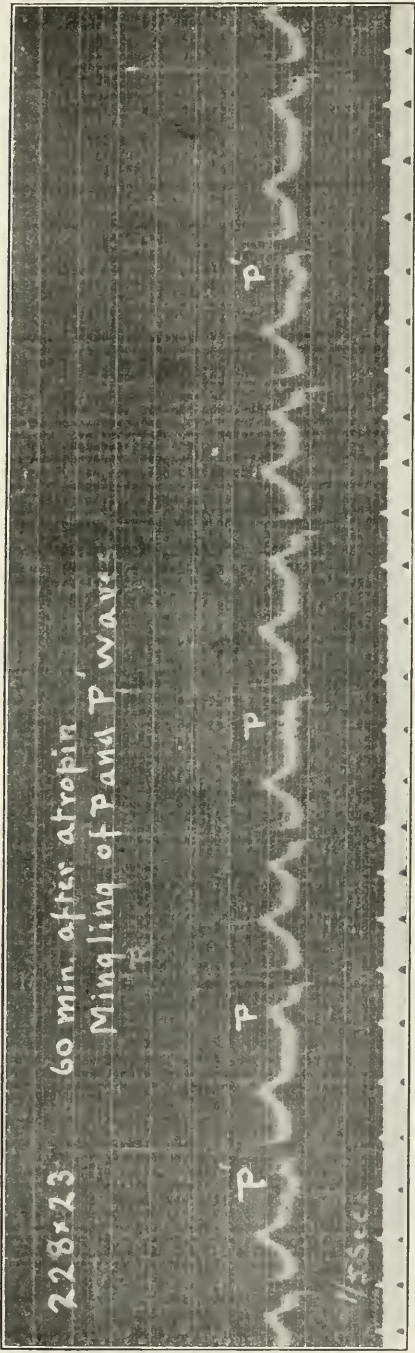
Fig. 7.—Electrocardiogram showing the mingling of the negative P wave and the normal auricular complex.

disturbed by a change in the vagus tone at the normal and ectopic areas due to vagus pressure. The point to be emphasized is that here, as elsewhere, there is manifested the influence of the vagus over the ectopic focus as well as over the sinus area. It may also be observed that here too the ectopic impulses fail to cause ventricular responses during the slow rate.

One phenomenon of interest that has not been mentioned was presented by this case during the second atropin experiment (No. 228). In Fig. 4 and in the table it is observed that when the ectopic beats began to occur regularly after every second normal beat, that is, when the vagus paralysis had become fairly well established, the time interval from the beginning of ventricular systole to the occurrence of the ectopic beat began to lengthen. In other words, the ectopic beats became further and further removed from the normal beats of the auricle preceding, until finally this time interval was nearly the normal interauricular interval and the ectopic beat occurred at about the time of the normal beat of the auricle (Fig. 7). When this took place the two contractions (whose stimuli arose in different foci) occurred together, one yielding on the record an upwardly directed wave, the other a wave directed downwardly; and the resulting record shows a small, irregular, in places almost iso-electric complex.

The constant relation of the ectopic auricular wave to the T wave of the preceding normal ventricular complex and the disturbance of this relationship under atropin paralysis are interesting features of this case. A discussion of the cause of this relationship, however, involves many hypothetical considerations, and will not be entered upon at this time.

SUMMARY. A case of cardiac arrhythmia caused by almost constantly occurring ectopic auricular contractions is described. The case has been studied especially in order to determine what influence the vagus nerves might have on the ectopic focus of stimulus production.

It has been found that stimulus formation in the ectopic focus is under the control of the vagi as well as in the normal pace-maker of the heart. The ectopic beat is inhibited when the vagus activity is increased, and occurs frequently and regularly when the vagus activity is lessened or removed. This fact has been observed by the study of electrocardiographic records made before and after atropin administration, exercise, and stimulation of the vagi by pressure. Changes in vagus influence at the ectopic focus accompanying sinus arrhythmia lead to the same conclusion. There is no conclusive evidence that the ectopic focus is under the control of one nerve more than the other.

The study of this case also emphasizes the fact that the time relationship of the ectopic beat to the preceding ventricular con-

traction may be an important factor in determining whether or not the ectopic beat of the auricle will stimulate the ventricle to contract, and whether this contraction of the ventricle caused by the ectopic auricular beat will yield a normal or aberrant complex in the electrocardiogram. Other factors than conduction changes may be important in this relationship, and the shorter time occupied by ventricular systole as the heart-rate increases, causing the refractory period to end sooner than it does when the rate is slow, is suggested as a factor in this case in allowing the ectopic beats to stimulate contractions of the ventricles when the rate is fast and not to cause ventricular responses when the rate is slow.

This case shows a splitting of the P wave of the electrocardiogram during periods of increased vagus activity which may be interpreted as due to a change in the location of the pace-maker. A record of auricular activity arising synchronously in two separate foci is shown.

The case seems worthy of record because it demonstrates that the vagi may be active upon an abnormal focus of stimulus formation. This vagus activity influences stimulus production in the ectopic focus as well as in the normal pace-making area of the heart.

I wish to express my appreciation of Dr. Robinson's unfailing interest and assistance in the study of these records, and to thank him for helpful suggestions in trying to arrive at a proper interpretation of them.

ETIOLOGICAL FACTORS OF ACNE VULGARIS.

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ALTHOUGH acne vulgaris is one of the most common of all cutaneous affections, yet the etiology of this disease has received insufficient attention at the hands of the dermatologists and practitioners.

Acne while not causing physical suffering, as a rule, may occasion an amount of mental distress and annoyance which is to some almost unbearable, and while it never endangers life it may often and does render existence so miserable that some individuals badly afflicted with it have even wished to die.

Statistics regarding the frequency of acne will vary, dependent upon the sources from which they are obtained.

The percentage of acne cases gathered from a dispensary practice where the vast majority of patients come from the poorer class falls very low, in the neighborhood of 3 or 4 per cent., because in this group of individuals acne is looked upon as a disfigurement which has to run its course and cannot be modified by treatment.

In the Polyclinic Hospital skin clinic out of 7150 patients treated during the last six years acne constituted 6 per cent. of all patients treated.

McCall Anderson among 10,000 dispensary patients in Glasgow reports 349 with sebaceous disease, or 3.4 per cent. Out of 74,455 cases of general skin disease collected by the members of the American Dermatological Association in six years there were 8088 patients with sebaceous disease, or almost 11 per cent.; among these were included those seen in private and public practice.

It is apparent from these statistics that acne stands next to eczema in its frequency among affections of the skin.

In a study of the etiology of acne vulgaris one is impressed with the importance of gastro-intestinal symptoms.

In the records of Bulckley almost 45 per cent. of the patients complained of constipation in some form. In our own records 35 per cent. of our acne patients complained of interference, with normal bowel movement.

Evidence of imperfect digestion in the upper portions of the alimentary tract is also very common in acne vulgaris. Various types of imperfect digestion may be alluded to: some exhibit a tendency to vomiting, some complain of heartburn, acid eructations, wind, heaviness in the epigastrium after a meal, and various other minor complaints. A coated tongue is often noted among acne patients. We have known of several instances of acne vulgaris developing after typhoid fever and after attacks of appendicitis.

Within the last year Lloyd W. Ketron and John H. King have studied the gastro-intestinal tract in acne vulgaris from the laboratory side. The studies pursued were fluoroscopy of the gastro-intestinal tract, test meals, and analyses of gastric contents.

Thirty patients suffering with acne vulgaris were studied, and their work shows that out of this number 93 per cent. showed some gastric abnormality while 70 per cent. showed intestinal abnormality. The most common gastric findings were hyperacidity 48.1 per cent., retention 36.6 per cent., atony 33.3 per cent., and ptosis 40 per cent. The most common intestinal findings were cecal stasis 46.6 per cent., ptosis of colon 36.6 per cent., and right lower quadrant adhesions 23.3 per cent.

The gastro-intestinal findings were found in a marked degree in 60 per cent. of the cases studied, and in a minor degree in the remainder 33 per cent.

The authors state that when the conditions which they found in the gastro-intestinal tract in acne vulgaris is marked it leads to toxic absorption, and they feel that this toxemia is probably a factor in acne vulgaris.

It is the belief of the authors that the well-established clinical observation as to the association of abnormalities of the gastro-intestinal tract with acne vulgaris has, in many cases, a well-founded pathological basis.

We have made an effort during the last two years to throw some light upon the nature of the intestinal flora in acne vulgaris so as to establish, if possible, a scientific basis for the intestinal origin of the majority of cases of this disease.

With this end in view the author conducted some gross experiments to determine if there was any difference in the fermentation properties and indol productions of the bacterial flora of the feces of patients with acne vulgaris and those of normal individuals. To this end the feces of 15 patients were studied, 9 with acne vulgaris and 6 controls. The diets in the different patients were noted, the feces collected in sterile jars, and the specimens either examined immediately or kept on ice.

The technic consisted in taking 10 grams of feces and dissolving it in 50 c.c. of sterile distilled water. From this solution 1.5 c.c. were inoculated in fermentation tubes, each containing 12 c.c. of the following fluids: water, bouillon, and glucose bouillon. Into a 150 c.c. flask containing peptone water 2 c.c. of the diluted feces were placed and incubated. The fermentation tubes were observed at the end of forty-eight hours and the peptone water flasks were studied about once every ten days for indol, using as reagents 15 per cent. H_2SO_4 and 0.5 per cent. sodium nitrite solution.

A study of the fermentation experiments in acne and in the controls discloses almost identical results in the acne patients and also in the patients devoid of eruption. The distilled water fermentation tubes showed a bubble, the bouillon tubes ran up to 0.4 per cent., while the glucose bouillon tubes were as high as 2 per cent.

In the indol experiments, out of the 9 acne patients, all of whom were on full diet, 5 gave positive indol reactions, 3 were negative, and in 1 case the flask was broken. Indol appeared in from two or three weeks in 4 cases and in one instance in one month.

In the control indol cases 4 patients who were on full diet did not show any indol production; three of these flasks were kept for three months and one for two months. Two of the patients were on semisolid diet, and in both of these indol was positive in about twenty-four days.

With the same object in view the author, in conjunction with Dr. John A. Kolmer and Dr. Jay F. Schamberg, performed complement-fixation tests on acne patients, using polyvalent antigens of colon bacilli isolated from acne patients, and also, as a control,

colon bacilla were isolated from normal persons not afflicted with acne. In all 57 patients with acne were studied, and out of this number 63.1 per cent. gave positive fixation with the colon acne while only 32 per cent. gave positive fixation tests with the colon normal. The degree of fixation was much stronger with the colon acne than with the colon normal. These serological findings would seem to indicate that disturbances of the gastrointestinal tract were factors in the causation of acne vulgaris, a fact long suspected on clinical grounds.[1]

We have recently studied the question of "food anaphylaxis in acne vulgaris." We tried this test in 14 patients afflicted with this disease, and while we obtained some positive reactions, in the large majority of patients the correction of the diet in accordance with the findings of the test did not show any favorable impression upon the acne.

It is our belief that the metabolic disturbance in acne is not along the lines of food sensitiveness.[2]

Age as a factor in acne has been known and emphasized for a long while. It is a well-established fact that puberty is an important predisposing factor in the development of acne. It is unusual to see acne before the eleventh or twelfth year, although we have recently observed a case in a girl, aged nine years. It can be stated that acne vulgaris is most common between the fifteenth and thirtieth years, although cases are observed until the age of forty years.

Just what is the causative relation between seborrhea in its various types and acne cannot be stated definitely. In our records there were 34 instances in which there were notes relative to seborrhea of the scalp and face among acne patients. Out of this number 20 did not have any seborrhea and 14 had this condition either on the face or scalp, or both.

It has long been maintained that anemia played a role in the etiology of acne vulgaris. We studied the hemoglobin and red cell count of 48 patients with the following conclusions:

1. Out of this number 8 patients showed a hemoglobin record varying from 60 to 80 per cent., with a corresponding red cell count; 3 were between 60 and 65 per cent.

2. Fourteen cases showed hemoglobin records varying between 80 and 90 per cent., while the remaining 26 patients had hemoglobin records varying from 90 to 96 per cent. The anemia manifested by these patients was of the chlorosis type.

A study of the sugar content of the blood in acne vulgaris shows the presence of hyperglycemia in a certain percentage of patients. In 30 cases of ordinary acne studied by Schwartz, Heimann, and

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[1] For further report see Complement-fixation in Acne Vulgaris, by Drs. A. Strickler, John A. Kolmer, and Jay F. Schamberg, Jour. Cutan. Dis., March, 1916

[2] For fuller report on food anaphylaxis in relation to acne see author's paper Food Anaphylaxis in Dermatology, with Special Reference to Eczema.

Mahnken 7 showed increased blood sugar, while in the 7 cases of indurated acne which these authors studied, none failed to show a hyperglycemia.

The urinary findings in acne are not of any great consequence. In our investigation and in the work of other observers excessive indican is found at times in acne. Bulckley in a study of 44 cases found nothing abnormal in the chemical study of the urine, while microscopically there was found in a comparatively few instances uric acid, urates, and oxalate of lime deposits.

In regard to the connection between disturbance of the utero-ovarian organs and acne in the female sex we have very much that is definite and accurate.

The onset of acne at the age of puberty, the increase or the appearance of the eruption of acne at each menstrual epoch, the persistence of the eruption in some cases until some mechanical uterine difficulty is removed, and the appearance or the aggravation of the eruption during pregnancy, as has been observed, all point to some relation between the condition of the female reproductive system and acne. It must also be recognized that there are thousands of women suffering from disorders which are commonly regarded as causative of acne without the occurrence of the eruption, while in many cases of acne no sexual disturbance can be discovered.

Bulckley in his analysis of 510 cases in whom there were recorded menstrual histories, concludes that in 191 nothing abnormal was stated; occasional disturbances were quoted in 60 and habitual derangements were recorded in 259 patients. The complaints among this latter class were very variable. A comparatively large number stated that their eruption was generally worse at each menstrual epoch, and some very few stated that it only appeared at that period. In our own records of 125 patients we have noted 5 instances in which there were menstrual disturbance of one kind or another. That female patients will often remark that their acne gets worse at the menstrual period can be attested by most dermatologists.

A few words must be stated in this connection as to the alleged relation between matrimony and acne. The authorities are at wide variance on this question. Some follow Plenck's dictum, "matrimonium varos curat," and some Hebra's assertion that "tempus varos curat," and the truth probably lies between the two extremes. While statistics seem to prove that acne is more common among those living in a state of celibacy than among those in a married state, yet most observers are of the opinion that married life has nothing to do with it. However, the state of matrimony entails better hygiene and more normal sexual life, all of which may reflect favorably upon the organism as a whole; and also married individuals are less apt to consult a physician in reference to a mild acne than those enjoying single blessedness.

The size of the thyroid gland was observed in 28 instances, and out of this number 7 showed glandular enlargement and 21 showed no change in the size of the thyroid gland. What relation this observation has to acne is difficult to say.

There remains for us to discuss the bacteriology of acne vulgaris from the view-point of cultural studies and smears and also along the lines of complement-fixation.

A study of the smears taken from acne lesions discloses the presence of acne bacilli in practically all cases in association with other cocci. Culturally it is possible in a percentage of cases to get a pure culture of the acne bacillus by the use of special media. Gilchrist in 96 cultures taken from pustules recovered the acne bacillus in 11 instances in pure culture, using a special medium. In our own work from some thirty efforts to obtain the acne bacillus in pure culture we were successful in three instances only. If the papules are utilized to obtain culture material it is more probable that the acne bacillus will be obtained than if the material obtained from the pustules be used. Gilchrist in his culture studies of the acne bacillus using the material obtained from papules found the acne bacillus in pure culture in 52 instances out of 145 lesions studied, and in 15 instances the acne and staphylococcus were found in mixed culture.

Schamberg has described a bacillus resembling the acne bacillus found in the sebum expressed from the follicles of the nose in normal individuals.

Etiological studies along the principles of the complement-fixation test were first reported by Haase, who stated that he obtained 6 positive results from the 10 cases he had studied.

In our own studies, in conjunction with Dr. John A. Kolmer and Dr. Jay F. Schamberg, in a series of 57 cases we obtained 48 positive results, or 84.2 per cent.

With the staphylococcus antigen we obtained in the same series 64 per cent. positive fixation, and there was no difference whether the staphylococci were obtained from acne lesions or from other pyogenic conditions.

CONCLUSIONS. If we should be asked what in our opinion is the cause of acne vulgaris we would answer that acne is a complex disease, with a great many factors to be considered.

1. Acne is due, in our belief, in the vast majority of instances, to the acne bacillus.

2. That this organism is probably normally present on the skin of individuals not subject to acne, but in those individuals who develop the disease the acne bacillus, is activated by other factors.

3. The activating factors are in a certain percentage of cases either the colon bacillus or its toxins, or both, as shown by the complement-fixation test and in a lesser degree by the staphylococcus or by both bacteria acting in conjunction.

4. To further substantiate the role of the colon organism in acne we have the indol experiments, which seem to indicate some variation in the behavior of the colon acne organism from that of our normal controls. These indol experiments are, of course, only suggestive.

5. It must be recognized that there are cases of acne due either to internal administration of certain remedies or to certain local applications.

6. We noticed in a certain percentage of acne patients an increase in the size of the thyroid gland. The exact significance of this fact cannot be definitely stated. Some writers are of the belief that an increase in the size of this gland is an indication of intestinal toxemia.

7. It is our belief that the use of cosmetics plays a role in the increase of this affection.

8. From our studies we do not see any relation between food anaphylaxis and acne vulgaris.

9. That among other factors puberty plays an important predisposing role.

10. Among other predisposing factors, seborrhea, anemia, derangement of the stomach, nervousness, and pelvic disease play a role of greater or lesser importance, but we feel that these never play the role as an exciting factor.

We wish to express our thanks to all those who have aided us in this work, my hospital associates and nurses, all of whom helped to accomplish the work herein recorded, and, as always, we wish to express our thanks to our chief, Dr. Jay F. Schamberg, for his untiring courtesy to me.

CHRONIC HEART-BLOCK.[1]

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AND

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We have had an opportunity to observe 9 cases of chronic heart-block during the past two and a half years. The effect of therapeutics in the last 4 cases seems worthy of presentation at this time because we have been administering a drug not hitherto mentioned

in cardiac treatment and have been apparently successful in increasing the idioventricular rate, with marked relief of symptoms.

Complete chronic heart-block is now recognized to be due in all cases to a functionally complete break in the auriculoventricular bundle. This failure of conduction is proved to be due to organic severance of the bundle in the great majority of all carefully autopsied cases, and we may assume that the few exceptions are failures in present methods of objective study rather than actual exceptions.

The pathology of chronic heart-block is too well known to justify elaboration. Inflammation and degeneration of the bundle, infiltrating gummata and neoplasms involving the bundle are the chief lesions described. Valvular disease or coronary sclerosis is usually present. Mitral disease is the most frequent valvular lesion.

The changes in cardiac rhythm progressing from a definite prolongation of the auriculoventricular interval to the dropped beat, then to the 2-1 and 3-1 rhythm and finally to complete dissociation of rhythm are now fully recognized. The Stokes-Adams syndrome results from circulatory changes which produce cerebral anemia, i. e., the syndrome may manifestly be due either to temporary stopping of the ventricles or in certain cases to little runs of rapid contractions which are inefficient in their pumping action. In certain cases the syndrome is brought on by exercise, since there is no compensatory increase in the ventricular rate. Cases have been reported in which complete block has existed for many years with little or no discomfort to the patient and in which no other organic lesion was evident. However, such cases as we have seen them, are the small minority. Most patients with chronic heart-block are confirmed cardiopaths and subject to the Stokes-Adams syndrome with its attendant dangers.

We know that the vagus gives branches to the sinus node and to the auriculoventricular bundle, and that stimulation causes slowing of the heart by inhibition of the sinus and of the conducting bundle. The cardiac accelerator nerves have a similar distribution, but they act to increase the sinus rate. So far as has been proved they cause no increase of the idioventricular rate. Digitalis is recognized as stimulating the vagus and thus slowing conduction in the bundle, though therapeutic doses often produce no rate reduction in a sinus rhythm or tachycardia. No drug or measure is known which increases the idioventricular rhythm, yet such result is manifestly desirable in chronic heart-block.

Thyroid extract will excite a tachycardia in the normal organism. Such effect is produced probably by action on the accelerators or a direct stimulation of the sinus node, though no experimental work is available to prove this action. A large mass of clinical evidence without laboratory proof shows that thyroid extract markedly affects the myocardium, as illustrated by the irritable and rapid

action with concomitant myocardial degeneration of the thyrotoxic heart.

During the examination of a case of chronic heart-block we thought of attempting to increase the idioventricular rate by the administration of large doses of alpha iodin, the active constituent of the thyroid which Kendall has isolated recently. The administration of this drug has been followed in 4 cases by marked improvement in the patients' nutrition, associated with increased ventricular rate and cessation of the Stokes-Adams syndrome, though one patient has since died. The histories of these four patients are briefly as follows:

CASE I (134644).—Male, aged forty-two years. No history of rheumatism, tonsillitis, chorea, or lues. Following diphtheria at twenty years he suffered from occasional palpitation and rapid heart action for a short time, but made a complete recovery. A slow pulse was noted at times for eight to ten years, but he was considered healthy until two and a half years before coming to the Clinic, when during an attack of measles his doctor found his pulse 42. The pulse had been slow ever since, averaging 37, and never being faster than 40. The patient suffered from occasional spells of "palpitation." He had gradually become dyspneic and unable to work, but had never been in bed. Two weeks previously he began having "sinking spells;" he suddenly became dizzy and his heart seemed to stop. He was momentarily unconscious without convulsions and with instant recovery. Any exertion brought on a spell. During the previous few weeks he had ten to twelve such spells a day.

Physical Examination. Blood-pressure 112–60. Pulse 36. Heart 6 inches to the left and a very loud, harsh systolic mitral murmur with heaving apical impulse.

Diagnosis. Bradycardia with mitral lesion, probably double, and myocardial insufficiency. Electrocardiogram showed complete dissociation with auricles 71, ventricles 36. Wassermann negative. The administration of $\frac{1}{30}$ gr. of atropin by mouth caused no change in the action of the heart.

Treatment. The patient was put on alpha iodin, 3 mg. daily, with prompt rise in auricular rate in five days to 88. On the tenth day the ventricular rate increased to 40. The spells disappeared after several days of treatment. For eleven months there were no spells and the pulse was 40 to 48 constantly. During this time he came to the Clinic five times for observation. The medicine then gave out, he had no treatment for a few days, and the spells (very violent) promptly returned. The pulse slowed to 32 and he came back for observation and treatment. When coming to the Clinic he fell on the street and cut his head. During the first few days 3 mg. of alpha iodin were given daily, and as before there were repeated hard spells with many little ones. After two weeks of treatment he was dismissed to continue medication at home. Five

months later he reported that he was doing light farm work and had
had no further spells. His ventricles now average 48 and auricles
105.
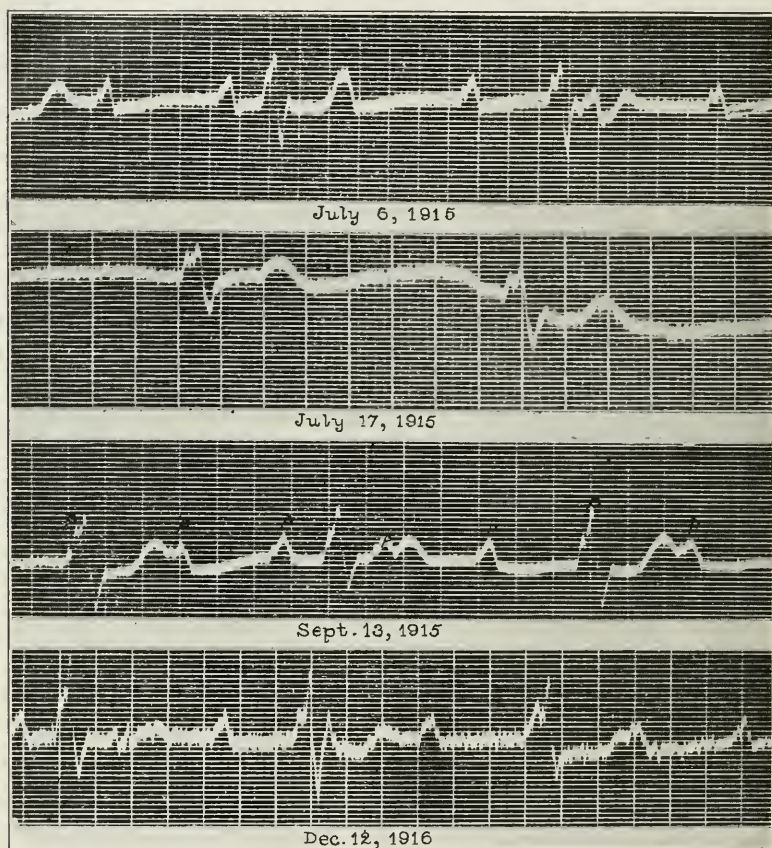
Fig. 1 (Case 134644).—Lead II. Complete dissociation. (1) Auricles 75; ventricles 32; alpha iodin administration begun; (2) auricles 83, ventricles 40; (3) auricles 106, ventricles 106; (4) auricles 105, ventricles 45.

This patient was relieved of symptoms during sixteen months
without relief of the block. The idioventricular rate increased, with
marked improvement in general nutrition and a gain of 15 pounds
in weight. His improvement apparently depends on continued
medication, evidenced by prompt return of the syndrome when
medication is stopped.

CASE II (173079).—Male, aged sixty-four years. No tonsillitis
or rheumatism. Denied venereal infection. He had had la grippe
twenty years previously, and following this, dyspnea and at times
pounding of the heart, but he entirely recovered. Three years

previously he began to be dizzy and was treated for heart trouble. Edema of the legs was noted two years later. Recently he had two fainting spells, possibly apoplectic. He had known of a very slow
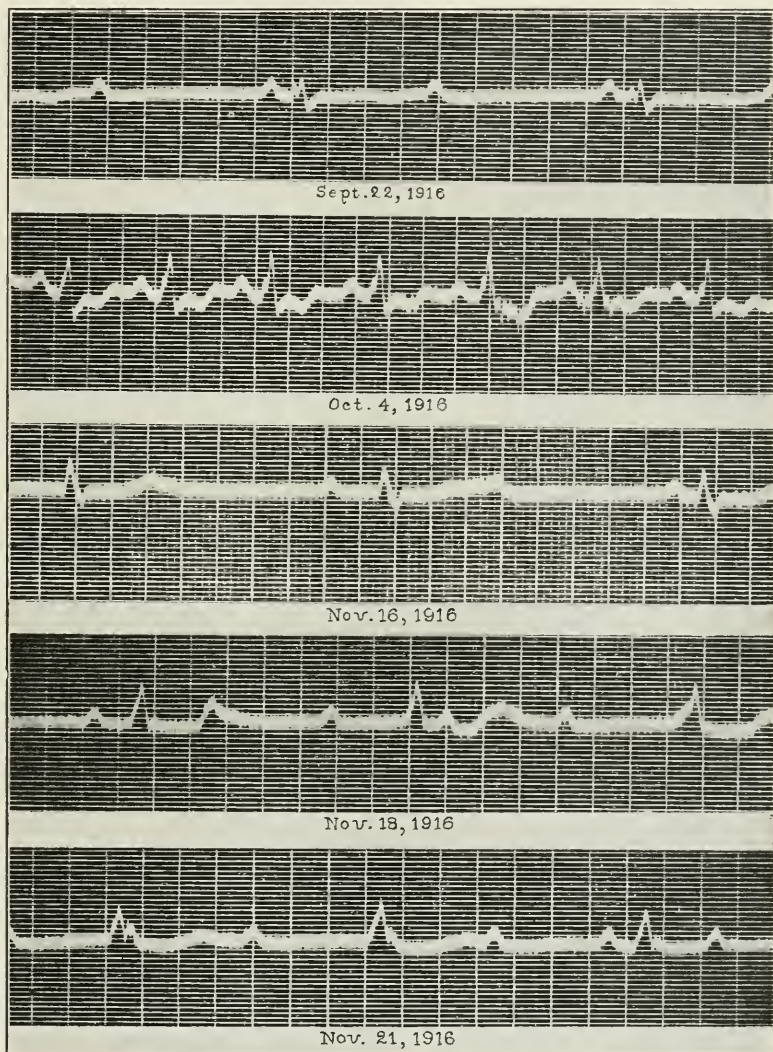
Fig. 2 (Case 173079).—Lead II showing: (1) Ventricles 32 with complete dissociation; (2) sinus rhythm reëstablished after alpha iodin; (3) complete dissociation reëstablished after medication was discontinued; ventricular rate 33; (4) ventricular rate increased to 40 under alpha iodin; and (5) ventricular rate 43 under treatment.

pulse for at least four months, and during this time exertion had caused "dizzy spells" lasting a few seconds. He immediately stopped exertion until he felt well again.

Physical Examination. Heart 5 inches to the left and 1 inch to the right; rate 30; loud systolic blow at apex. Eye-grounds showed arteriosclerotic vessels and rather hazy disks. The brachials were very sclerotic. Electrocardiogram showed complete block, with auricles 66, ventricles 32. Wassermann negative.

Treatment. Digitalis, 20 drops, three times a day, and alpha iodin, 2 mg., was begun September 25, 1916. September 28 sinus rhythm (rate 90) was restored, but with marked evidence of impaired intraventricular conduction, as evidenced by the widespread *R* wave. Medication was discontinued on October 5, and during one week of observation the sinus rhythm was maintained. The patient went home for a month, then returned, with his block reëstablished for one week. He was again placed on the same treatment, and his ventricular rate increased from 32 to 44 in a few days. He again asked to go home for a day and the next morning, at his home, dropped dead. Permission for necropsy was not obtained.

It is evident that in this case the block was functionally but not anatomically complete. The increased irritability produced by the alpha iodin appears to have relieved the functional block by increasing the irritability of the junctional tissues along with the myocardium. After medication was stopped the relief continued for four weeks, with marked subjective improvement. The block recurred, however, and the patient died suddenly twenty-two days later in spite of the fact that his ventricular pulse was again responding to the treatment.

CASE III (145901).—Male, aged sixty-one years. Neisserian infection twenty-five years previously and lues questionable. Wassermann negative. He complained of stiffness of the spine and dizziness on exertion. The cardiac history was of four to six years' duration. He had attacks of an "all-gone feeling," extending from stomach to neck, and momentary dizziness. Such attacks usually followed exertion, but occasionally came on at other times.

Physical Examination. General condition fair. Pulse 36 to 40. Heart 4½ inches to the left, with loud systolic blow over the whole pericardium. There were a very marked spondylitis deformans and a large right branched kidney stone. The dental roentgenograms were negative. Electrocardiogram showed complete block with auricles 107, ventricles 41.

Treatment. Operation for the kidney stone was obviously not indicated. After observation in the hospital for five days, during which time the pulse averaged 41, with 32 and 50 as extremes, the patient was given alpha iodin, 3 mg. daily. On account of nervous symptoms this amount was dropped to 1 mg. on the seventh day and the observation continued for eleven days while alpha iodin was given. During this time the pulse averaged 44, with 32 and 60 as extremes. At this point, in spite of improvement, subjective and objective, the patient was obliged to leave the Clinic. A month

later his brother, a physician, wrote that he had had no further dizzy spells, but it had been necessary to reduce the dose of alpha iodin on account of nervous symptoms.

CASE IV (163350).—A married woman, aged twenty-five years. No venereal history. Wassermann not taken. She had had repeated attacks of tonsillitis. Three years previously she fell and struck her lower back. The pain was very severe for a week and was then relieved by the discharge of a large quantity of pus through the rectum. A week later she had an attack of tonsillitis, and after a week of illness she began vomiting repeatedly and had repeated fainting spells. A physician was called who found her pulse 28. There was a fair recovery from symptoms and the patient was in fair health except for dyspnea for a year. One morning she suddenly fell over and remained unconscious for nearly an hour. During this time she was said to have been very blue and to have had a very slow pulse. Since then, two years before coming to the Clinic, she had had repeated sinking spells, with slow pulse, usually brought on by exertion.

Physical Examination. The heart was $4\frac{1}{2}$ inches to the left and the pulse 42. Blood-pressure 158–78. The beats were irregular and there was a faint systolic murmur at the apex, with only slight transmission toward the axilla. The tonsils were moderately enlarged, with marked evidences of chronic tonsillitis. An electrocardiogram on the first day showed a ventricular rate of 60, due to repeated ventricular extrasystoles, with auricles 92.

Treatment. One-half mg. alpha iodin was administered daily. The auricular rate rose within five days to 120 and within nine days to 180. The ventricular rate averaged 45 to 48. The patient then left the Clinic. Eight months after the beginning of the treatment she wrote: "My health is fine and I am gaining every day. I can do as much work as the average woman, and not get very tired either."

In this case there was complete cessation of the Stokes-Adams syndrome for eight months after two years' duration, during which time it had occurred often. Circumstances prevented a closer study of the ventricular rate, but the result seems fairly conclusive when studied with other cases.

In addition to these 4 cases there have been 5 other patients observed but not treated since November 1, 1914. The total number of cases, 3 women and 6 men, may be summarized as follows: One patient was twenty-five years of age, 2 were in the forties, 1 in the fifties, and 5 in the sixties; 1 gave a history of gonorrhea, but none gave histories of syphilis; 6 showed negative Wassermanns. Only one patient had a history of rheumatic fever; 2 others admitted vague rheumatic pains. In 2 instances the trouble seems to have followed diphtheria, and la grippe may have been the etiological factor in 4; 7 of the 9 patients gave a history of the Stokes-Adams

syndrome, and all but 1 had cardiac murmurs; 3 of these showed clinical predominance of an aortic lesion and 5 predominance of a mitral lesion. Of the 7 patients concerning whom word has been received recently, 3 are dead, all dying in typical Stokes-Adams attacks.

SUMMARY. 1. Alpha iodin quickens the idioventricular rate in complete heart-block. This is followed by marked subjective relief to the patient. The drug must be pushed to the tolerance of the patient and the dose then reduced to the largest amount that can be taken without discomfort. The auricular rate increases much earlier and to a much higher figure proportionately than the ventricular rate.

2. In 9 cases of complete heart-block 8 patients gave evidence of definite valvular disease, mitral disease predominating. The ninth patient had advanced nephritis.

3. In none of these 9 cases was there a probable venereal etiology.

4. Six of the patients gave a history of probable etiological infections with the streptococcic group, i. e., chronic arthritis (1 case), la grippe and tonsillitis (5 cases). Diphtheria seems to have been responsible in 2 instances. The ninth patient did not give a history to previous infection on careful inquiry, but at autopsy a large mulberry calcified nodule was found involving the bundle and one cusp of the aortic valve. No other pathology was evident.

5. Digitalis should be used in all cases of chronic heart-block in which there is evidence of myocardial insufficiency.

6. We do not know the effects of long-continued administration of large doses of alpha iodin in patients not suffering from thyroid insufficiency. Therefore we believe that for the present this medication should be used only to relieve the Stokes-Adams syndrome in chronic heart-block.

VITILIGO AND SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.

By E. MURRAY AUER, M.D.,

CENTRAL INDIANA HOSPITAL, INDIANAPOLIS, INDIANA.

VITILIGO, characterized by an irregular, patchy distribution of the pigment matter of the skin, in which smooth, white patches of varying size and extent are produced, surrounded by an area in which the pigment is augmented, has long been known, but it is only recently that attention has been drawn to the frequency of its occurrence in syphilitic individuals.

In 1889 Tennesen reported the case of a syphilitic in whom there developed a vitiligo of the head, trunk, and lower limbs. Ducastel, in 1892, suggested the possible relationship between vitiligo and

syphilis, and Thibierge, in 1905, again raised the question of such a relationship. Pierre Marie and Crouzon[1] reported a case in which there appeared simultaneously a syphilitic eruption and vitiligo, and stated: "It is interesting to note another example of this manifestation of syphilis, since cases of vitiligo are sufficiently rare, and despite their observation the relationship between vitiligo and syphilis is not well known." In their presentation of a case exhibiting the simultaneous development of vitiligo and tertiary syphilides, Gaucher, Gougerot and Auderbert[2] differentiated these two conditions and demonstrated that vitiligo was not succedent upon other syphilitic skin manifestations. Bacaboglu and Parhon[3] reported a case of vitiligo of congenital origin in a patient presenting, together with many syphilitic manifestations, several isolated patches of vitiligo and a more extensive girdle-like area, and observed that this segmental distribution occurred with a bilateral lesion of the groups of origin of the sympathetic fibers in a definite region of the spinal cord. In the consideration of a case of syphilitic spastic paraplegia with generalized vitiligo, Guillain and Laroche[4] maintained that while vitiligo occurred in other conditions, the relation of this cutaneous lesion to syphilis was indisputable. Crouzon and Foix[5] in the discussion of a case of hereditary syphilis in a young girl, aged nineteen years, in whom vitiligo had appeared at the age of ten years, raised the question of the possible syphilitic origin of certain juvenile forms of vitiligo. Merklen and Leblanc[6] maintained that "if it was extreme to attribute vitiligo to syphilis its presence in an individual ought to serve as a possible indication of syphilis." The presence of vitiligo in a case of hereditary syphilis presenting a right hemiplegia and epilepsy was noted by Etienne.[7] Zelenev[8] from the statistical study of 52 cases of vitiligo considered etiologically two forms of vitiligo, tubercular and syphilitic. Dejerine[9] stated that vitiligo was sometimes seen in tabes.

While it is true that vitiligo has been reported as occurring in exophthalmic goitre (Trousseau, Raymond, etc.), after a psychic trauma (Dejerine), with chorea (Mallinckrodt), after an attack of scarlet fever (Hill), and with keratoma palmaire (Friedländer), yet the presence or absence of syphilis in the individual had rarely been sought for.

CASE I.—N. G., a while male, aged thirty years, was admitted to this institution July 20, 1916. Diagnosis: taboparesis. He had a history of syphilitic infection at nineteen years of age. On examination it was found there was marked dementia, anisocoria,

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[1] Bull. et mém. de la Soc. méd. des hôp. de Paris, Juillet 11, 1912.
[2] Bull. de la Soc. franc. de dermatographie et syphilographie, Mai, 1913.
[3] Nouv. iconog. de la Salpêtrière, Juillet-Aout, 1913.
[4] Bull et mém. de la Soc. méd. des hôp. de Paris, Janvier, 1914.
[5] Ibid., Mai, 1914.   [6] Ibid.   [7] Ibid.
[8] Jour. russe des mal. cutan. et vener., Juin, 1915.
[9] Semiologie des affec. du système nerveux.

Argyll-Robertson pupil, speech defect, and the knee-jerk was found to be present on the right on reinforcement but absent on the left. Neither Achilles-jerk was obtained. There was no ataxic manifestations in the upper or lower limbs and no disturbances of the deep or superficial sensations. Vitiligo was marked over the back of both hands and on the back of the neck, and is said to have dated from early in the year 1914. The Wassermann of the blood was strongly positive. The spinal fluid was clear, with 177 cells per cubic millimeter. The Wassermann was strongly positive. The Noguchi test was positive and Lange's colloidal gold curve read 5–5–5–5–5–5–5–5–4–2. His physical examination was negative.

CASE II.—J. B., a white male, aged thirty-one years, was admitted to this institution February 19, 1915. Diagnosis: paresis. The patient is said to have had a specific infection in 1912. On examination it was found that the pupils were irregular, unequal, and reacted poorly and within narrow limits to light, but promptly in accommodation. The knee-jerks and Achilles-jerk were exaggerated, more markedly so on the right side. There were no sensory disturbances. The patient frequently complained of severe pains of a transitory character in the legs. He was hallucinated, disoriented, mentally deteriorated, and had no insight into his condition. He exhibited exaggerated ego, ideas of grandeur, influence, and persecution of a paranoid type. The Wassermann reaction of the blood was strongly positive. The spinal fluid was clear, with 51 cells per cubic millimeter, and the Wassermann was strongly positive. The Noguchi test was positive and Lange's colloidal gold curve read 5–5–5–5–5–5–4–2–1–0. There was an extensive vitiligo over the chest, said to have made its appearance four or five years ago. The physical examination was negative.

CASE III.—J. M., a white male, was admitted to this institution May 11, 1915, at which time he was possessed with the idea that he had many great inventions that would astonish the world, and would like to live to be as old as Methuselah so as to show the people that there was another great man besides the prophet. There was an exaggerated ego and ideas of persecution. No hallucinations were elicited. His papers stated that he had patents which he wished to lay before the President to stop the European war, that he wanted to marry the President's daughter, had great ideas of wealth, and would build an enormous hotel in the country. He gave a history of previous primary and secondary syphilitic manifestations of inexact date. On examination there was no motor disturbance evinced in walking or standing or in any of the finer tests of the upper or lower limbs. There was no ptosis or facial palsy. The pupils were unequal, irregular in outline, and the right pupil was eccentric. Both pupils reacted sluggishly to light, the right more than the left, but promptly in accommodation. On repeating the test phrases he showed tremor of the lips, hesitancy, reduplica-

tion, and omission of syllables. The deep reflexes of the upper limbs were present, prompt and equal. The knee- and Achilles-jerks were exaggerated, more so on the right side. There was no patellar or ankle clonus, no Babinski or Oppenheim reflexes, and no disturbance of the superficial or deep sensations. There was a well-marked vitiligo about the neck, over the dorsal surface of both hands, and well up over the extensor surface of the forearm and elbow. There was extensive vitiligo about the genitalia, spreading down almost to the knee or the internal surface of the thighs. On the scrotum the hair on the clear areas was gray while that of the pigmented areas was brown. Vitiligo first made its appearance on the hands ten years ago. On October 26, 1916, the Wassermann of the blood was doubtfully positive. The spinal fluid was clear under normal tension and contained 4 cells per cubic millimeter. The Wassermann was negative. Pandy's test was positive. There was a small amount of albumin, and Lange's colloidal gold curve read 0-0-5-5-5-5-4-3-0-0.

CASE IV.—R. W., a white male, was admitted to this institution October 24, 1911, at which time he is said to have been discontented, had no control over himself, thought everyone his enemy, and wanted to start in business. He gave a history of a syphilitic infection at twenty-one years of age. In 1896, at thirty-eight years of age, he suffered a left hemiplegia, at which time he was given anti-specific treatment. From 1904 to 1910 he was confined in the Richmond State Hospital. From February 15, 1913, to March 17, 1913, he received three intravenous injections of neosalvarsan. Previous to this there was a positive Wassermann on the blood and spinal fluid. On recent examination the patient in walking exhibited a hemiplegia of the left side. His station and gait were good, with the eyes open and closed; he wrinkled both brows equally well, and there was no ptosis or facial palsy. The pupils were central, irregular in outline, and reacted promptly to light direct and consensual and in accommodation. The tongue was protruded straight in the median line, and there was no defect of speech. The grip of the right hand was slightly better than that of the left. There was tremor of the hands on extension, more marked on the left side, and in the performance of the synergic tests of the upper limbs there was slight tremor of the left hand but no overlapping. The tendon reflexes of the upper limbs were present and prompt, with no appreciable difference of the two sides. The knee- and Achilles-jerks were exaggerated, more so on the left side, and there was a positive Babinski on plantar irritation of the left foot. There was no ankle clonus. Stereognostic perception was unimpaired, and there was no disturbances of the deep or superficial sensations. The physical examination was negative except for slight evidence of a beginning arteriosclerosis of the radials. The patient had never suffered dizzy spells or headaches. There were copper-colored scars over both

shins. Vitiligo was well marked over the neck, extending up on to both cheeks. There were a few areas over both scapulæ, and the dorsal surface of both hands extending over the elbow and extensor surface and pronounced vitiligo over the glans penis, but not about the scrotum, perineum, or thighs. The onset of the condition could not be accurately ascertained. October 26, 1916, the Wassermann on the blood was negative. The spinal fluid was clear under increased tension and contained 5 cells per cubic millimeter. The Wassermann on the fluid was negative. Pandy's test was positive, there was a small amount of albumin present, and Lange's colloidal curve read 0–1–5–5–4–3–3–2–0–0.

The cytological and serological findings of the last two cases are of interest, since despite the clinical manifestations neither showed an increased cell count nor gave a positive Wassermann reaction, while the globulin and albumin tests were positive and the colloidal gold curve read decidedly in the "luetic zone." By many such an occurrence is considered as foreshadowing a latent lues. Lee and Hinton considered the colloidal gold test as more delicate than the Wassermann reaction, and in view of this they with many others expressed the belief that reactions typical in the luetic zone confirmed the clinical suspicions of syphilis of the central nervous system even though the Wassermann reaction was repeatedly negative.

Miller and Brush in the examination of 252 spinal fluids from cases of syphilis of the central nervous system failed to find the combination of a positive Wassermann reaction with a negative or weak colloidal gold reaction, and further stated there can be no doubt that a strong gold reaction occurred when the Wassermann reaction was absolutely negative.

From a study of the results of these different observers one may conclude there is no apparent relation between the colloidal gold curve and the cell count, but that there apparently existed a close relationship between the increased globulin content and a positive colloidal gold reaction.

In conclusion I wish to draw attention to the early occurrence, as compared with the other symptoms, of the skin manifestations, the appearance of which should make one strongly suspect a syphilitic condition in the individual, and, further, to the symmetrical and segmental distribution of the areas suggesting a lesion of the central rather than of the peripheral nervous system.

REVIEWS

The Treatment of Diabetes Mellitus, with Observations
upon the Disease Based upon One Thousand Cases. By
Elliott P. Joslin, M.D., Assistant Professor of Medicine,
Harvard Medical School; Consulting Physician, Boston City
Hospital; Collaborator to the Nutrition Laboratory of the
Carnegie Institution of Washington, in Boston. Second edition.
Pp. 440; illustrated. Philadelphia and New York: Lea & Febiger,
1917.

The second edition of this work, appearing so shortly after the
first, bespeaks its warm reception. It is the fruit of nineteen years
of practice, in which 1300 cases of diabetes were treated. It presents,
very clearly, the recent advances in the treatment of diabetes, and
being based on personal observations, is of distinct practical value,
the author stating in the preface of the first edition that he has
honestly tried "to let the 400 fatal cases tell their useful lessons to
the 600 living." The volume is divided into seven sections. Section
I presents statistical studies upon the course and treatment of
diabetes mellitus. The statistics, offered in concise form, present
very strikingly the increase in the incidence of the disease as well as
the recent great improvement in the treatment. Heredity, etiology,
cause of death, etc., are also discussed with tabulated data included.
Section II deals with the important factors in treatment, empha-
sizing particularly the value of physical exercise and fasting. Hyper-
glycemia is well presented, tables adding materially. Blood fat,
metabolism, and then the nature of diabetic acidosis and its relation
to coma are discussed in turn.
Section III covers the examination of the urine, blood, and
respiration. The contents of this section contain much of interest
to both clinician and laboratory worker, for the most recent and
most useful tests are described, including, for example, Bang's
method for blood-sugar, tests for the carbon-dioxide tension in
alveolar air, etc.
Section IV, after a discussion of the diet in health, takes up the
diet in diabetes more in detail. Many suggestions are given, valu-
able alike to the physician and patient.
In Section V will be found the treatment. Under prophylaxis
are considered the early diagnosis, heredity, obesity, infections,
pregnancy, etc. Next the classification for treatment and for

prognosis is followed by dietetic treatment based more upon recent advances. Fasting receives much emphasis. The author next discusses the management of mild and of severe cases, "follow-up methods," cases unsuccessfully treated by fasting, and special dietetic methods. The treatment of acid intoxication emphasizes particularly the importance of prevention and the treatment of threatening coma. Complications, surgery, pregnancy, etc., receive their share in the well-rounded methods of treatment.

Section VI, on aids in the practical management of diabetic cases, contains much that the patient should know, the author speaking of it as his "diabetic's primer," and only "regrets that it is not still simpler." This section is an equally useful one for the nurse. Various charts, including one for history and another for dietary and urinary records, are good. Actual diets employed to render patients sugar- and acid-free are given, with a few notes concerning the individual cases which lend an interesting personal trend, as indeed does the frequent reference to individual cases throughout the volume. Both hospital and ambulatory treatment are considered in detail.

Section VII cannot be too highly recommended, containing, as it does, so much of practical value in the discussion of foods and their composition. American food materials, composition of diabetic foods, receipts, menus, tables of equivalents, etc.

The arrangement of the subject matter is systematic throughout, the tables and charts, headings and subheadings rendering the book most convenient for either rapid reference or study.

Much in the first edition has been condensed, illustrative tablets revised, new tables added, and fresh material included. A record of the subsequent history of most of the cases mentioned in the earlier edition increases the interest of this volume.

In conclusion, I know of no recent book on diabetes mellitus that is of more value to the practitioner. It is a credit also to the publishers.   A. H. H.

PROGRESSIVE MEDICINE. A QUARTERLY DIGEST OF ADVANCES, DISCOVERIES AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES. Edited by HOBART AMORY HARE, M.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Philadelphia, etc. Assisted by LEIGHTON F. APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia, etc. Vol. I, March, 1917. Pp. 314; 23 illustrations. Vol. II, June, 1917. Pp. 355; 97 illustrations. Philadelphia and New York: Lea & Febiger, 1917.

THE first volume of this well-known and widely read review of medical and surgical progress for 1917 appeared in March. It opens

with a very interesting discussion of the surgery of the brain by Dr. Charles H. Frazier. He follows this by an able article on the pineal and pituitary bodies, and gives a careful *résumé* of the recent literature on these subjects. He then takes, by a consideration of brain tumors, brain punctures, fractures, and wounds of the skull, and follows this with a discussion in detail of the recent advances in surgery of the face, jaws, neck, and thyroid gland. The article concludes with a consideration of the literature on the mammary gland.

Dr. George P. Müller contributes an instructive article on surgery of the thorax, the first part of which is devoted to injuries of the heart and chest during war.

Dr. John Ruhräh contributes his usual interesting and careful article on infectious diseases, thirty-five pages of which are devoted to poliomyelitis.

Dr. Floyd M. Crandall discusses at length diseases of children and devotes a third of his article to infant foods and feeding.

Dr. George M. Coates reviews the literature on rhinology, laryngology, and otology in a very thorough manner, and particularly discusses diseases of the accessory sinuses and sinus operations.

Vol. II opens with an instructive article on hernia by Dr. William B. Coley, in which he discusses the subject at length.

Dr. John C. A. Gerster then follows with an article on the various forms of gunshot wounds of the abdomen in war. Other operations on the stomach, duodenum, and intestines are discussed at length. The literature on surgery of the rectum is given a careful review, and the remainder of the article is devoted to a discussion of the surgery of the liver and bile passages and of the spleen.

Dr. John G. Clark then gives us his careful and complete review of recent progress in gynecology, and devotes the first twenty-seven pages to cancer of the uterus. Other conditions of the uterus are then taken up and carefully considered. He discusses in detail the non-malignant conditions of the uterus, diseases of the Fallopian tubes, ovaries, vulva, and vagina, and gynecological pathology and diseases of the female urinary system are taken up in turn. Syphilis of the female genito-urinary system is considered in the last part of the article.

Dr. Alfred Stengel gives us in his article on diseases of the blood, diathetic and metabolic diseases, diseases of the thyroid gland, spleen nutrition, and the lymphatic system a very comprehensive review of the literature on these different subjects. Diseases of the blood is very fully discussed in forty-two pages of the article, the remainder of which is devoted to a discussion of diabetes.

The last article in Vol. II is contributed by Dr. Edward Jackson on ophthalmology, in which he discusses, in his usual painstaking manner, the various phases of diseases of the eye.   S. S.

A Practical Text-book of Infection, Immunity and Specific
Therapy, with Special References to Immunological
Technic. By John A. Kolmer, M.D., D.Ph., Instructor of
Experimental Pathology, University of Pennsylvania. Pp. 899;
143 original illustrations, 43 in colors. Philadelphia and London:
W. B. Saunders Company.

This work is of convenient size, and is printed in clear type on
good paper. The subject matter is divided into five parts, dealing
with, first, general immunological technic; second, principles of
infection; third, principles of immunity and special immunological
technic; fourth, specific therapy; fifth, experimental infection and
immunity.

Part I is of peculiar interest to the student and the laboratory
worker. It is given over to a description of the equipment for sero-
logical work, drawing of pipettes, care of glassware, collection of
human and animal blood and fluids, methods of animal inoculation,
production and preservation of immune sera, etc.

Part II contains a clear presentation of the subject of infection,
the mode of infection, and the action of the various infective agents.

Part III covers the theory of immunity, the different types of
immunity, the study of opsonic index, and the preparation, standard-
ization, and administration of bacterial vaccines and the preparation
of antitoxins and antivenoms. Ferments and antiferments and the
technic of the Abderhalden reaction are thoroughly considered.
This chapter needs to be brought up to date, as the ideas as to the
mechanism of specific ferment action are daily changing. The
various agglutinative and lytic phenomena and cytotoxins, colloids,
and anaphylaxis are each given a separate chapter. The subject
of complement-fixation, and especially the Wassermann reaction, is
covered in three chapters. In dealing with the subject of antigens
not enough stress is laid upon the danger of false positive results
with the use of cholesterin reinforced antigens, although the author
admits an error of about 5 per cent. positive reactions with speci-
fically negative sera. While it is true that it is desirable, as nearly
as possible, not to get negative results in any case of syphilis, the
possibilities of disastrous results from a false positive reaction are
so great that a positive result with cholesterinized antigen should
never be reported as "Wassermann positive" in the face of a negative
with a satisfactory specific liver antigen, except possibly, in treated
cases of known syphilis. It has an undoubted value in the case of
sera which give a "delayed negative" result with specific liver
antigen.

The list of "ordinary doses for adults of the various bacterins,"
as given in Chapter XIII, would appear entirely too large, at least
for the minimum doses given. The reviewer has seen at least one
with a severe reaction to a dose of 20,000,000 of Staphylococcus

aureus vaccine, the minimum dose for which organism is given by Kolmer as 100,000,000. The minimum dose for the other organisms in the list is proportionately high. No mention is made of the sensitivity of the individual to foreign protein. It is advisable to inquire into the sensitivity to pollen, animal protein and reaction to any previous vaccination in every case to be inoculated with bacterial vaccine. The presence or absence of sensitivity to foreign protein indicated by the answers to such questions are often very helpful in deciding on the primary dose to be administered.

Part IV contains chapters on anaphylaxis, vaccine therapy, serum therapy, and chemotherapy.

Part V, dealing with experimental infection and immunity, is of special value to the student, and takes up experimentally all the principal problems covered in the first four parts.

The index is quite complete, and so far as I have been able to observe there are no mistakes in its reference to the text. The many illustrations are excellent and add very materially to the text, although the style throughout is so simple and clear as not to need much illustrating.   H. F.

Some Personal Recollections of Dr. Janeway. By James Bayard Clark. Pp. 36. New York: G. P. Putnam's Sons, 1917.

It is marvelous how vivid an impression of the essential character of a great man these few pages give. His was a life in the words of the author, "A life worth knowing about for those with ideals; a life to study for those who are sincere; a life with a lesson for every student of medicine." For all such this little book will be a delight and an inspiration.   O. H. P. P.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Report of Studies Concerning Acute Lobar Pneumonia. — The method and results of the treatment of acute lobar pneumonia by sera are discussed by COLE (*Jour. Am. Med. Assn.*, 1917, lxix, 7, p. 505). In the Rockefeller Hospital they have determined the type of infecting organism in over 500 cases and have found that about 33 per cent. of the cases are due to infection with Type I pneumococci, 33 per cent. to Type II pneumococci, 10 to 15 per cent. to Type III, and the remainder to infection with pneumococci of Group IV. The mortality in infections with the various types seems to be of average severity in Type I and II, or about 25 per cent. to 30 per cent.; in severe infections with Type III about 50 per cent.; the cases in Group IV are milder, the mortality usually ranging from 10 per cent. to 15 per cent. The determination of the type of infecting organism and of the grade of the infection as evidenced by the number of colonies per cubic centimeters in the blood plates are of value in prognosis. The use of sera in treatment has shown that the serum made for infections with Type II pneumococci is of low potency and consequently of little value in the treatment of the disease. However, the serum for the Type I cases has given very satisfactory results. In a series of 105 cases of this type treated by serum in the Rockefeller Hospital only eight died, and of these there were only two in which the serum was adequately applied, or in which any success could have been expected from this form of treatment. During the past winter 35 cases were treated of which only two died. The treatment requires the determination of the type of infecting organism, as polyvalent sera should not be used, because the serum reactions should not be risked unless it is known that the serum

is potent for the particular type of pneumococcus involved. The method of determining the type of infecting organism is complicated, but not greatly so, and may be carried out in any place where cultures may be examined for the diphtheria bacillus. The treatment should be begun as soon as the case has been proved to be due to Type I pneumococci, as any delays are unjustifiable. The serum should be known to be of proper strength and potency, and should not be used unless guaranteed to be so by a reliable manufacturer. This serum should be administered intravenously, preferably diluted once with freshly prepared sterile salt solution. The patient should receive in the first dose 75 to 100 c.c. of the serum, and, if necessary, it should be repeated every six or eight hours until a favorable result is obtained. The average dose used in the author's cases last winter was 250 c.c. Usually within an hour or two after the injection there is a slight rise of temperature followed by a marked fall. Frequently after eight or more hours the temperature begins to rise again; the cases should be carefully watched, the temperature taken every two hours, and as soon as this rise appears, the dose of serum is repeated. If no change occurs following the first administration, the second injection should be given at the end of six or eight hours. Clinical and experimental evidence indicates that the treatment should be persevered in, even though no reaction is obtained after several doses. The danger of serum reactions may be eliminated to a great extent by careful administration of the serum. The first group of serum reactions are those immediately following the injection and are analogous to the anaphylactic phenomena in sensitized animals. Cole makes it a rule to inject into the skin of every pneumonia patient upon admission, 0.5 to 1 c.c. of horse serum. If the patient is sensitive to horse serum a reaction appears about the site of injection in an hour or two, and by the time the type of infecting organism has been determined (twenty-four to forty-eight hours) the patient is largely desensitized. Then, when the serum is injected, it is introduced very slowly, fifteen minutes being allowed for the injection of the first 15 c.c. If no reaction has occurred (tachycardia, restlessness, suffusion of face, dyspnea or urticaria), the remainder may be given rapidly. If the skin test has shown the patient to be sensitive, additional measures must be taken to desensitize the patient. This is accomplished by beginning with small doses of the serum, repeated often, and gradually increasing the size of the dose. Care should also be taken with patients who are known to suffer from asthma, hay fever or other forms of protein sensitiveness. The second group of reactions are those similar to the reaction sometimes seen after salvarsan injections, and have symptoms similar to the first group. These are non-specific protein intoxications and will occur occasionally. Some lots of serum are more liable to produce them, and these sera should not be used. If an attack supervenes, 0.5 c.c. epinephrin or 0.01 grain of atropin usually gives relief. The last group of reactions are those occurring usually from seven to fourteen days following the injections of serum, and are the reactions grouped under the term "serum sickness," consisting of fever, skin rashes, glandular enlargements, edema of skin and joint pains. Mild symptoms occur in about half the cases treated, severe ones rarely. They are distressing, but are always recovered from without sequelæ. The urticaria is most distressing, and is temporarily relieved by injec-

tions of epinephrin, and the itching by phenol washes. The physician should look carefully for the appearance of complications of pneumonia, and not carelessly ascribe fever, etc., to "serum sickness." Hospitals and certain health boards are prepared to determine the type of pneumococcus in any case, and the serum is now being produced by some of the big commercial houses, so that the serum treatment in Type I cases should be used widely, the danger from any untoward results from the serum being negligible when compared to the benefit to be derived from its use.

Visceral Disturbances in Patients with Cutaneous Lesions of the Erythema Group.—CHRISTIAN (*Jour. Am. Med. Assn.*, 1917, lxix, No. 5, p. 325) discusses the group of cases exhibiting various symptoms on the part of the viscera, but showing in common skin lesions of the erythema group. Diagnostic mistakes are often made; abdominal symptoms may lead to needless laparotomies, and hematuria may suggest surgical conditions of the kidney or nephritis. Renal changes similar to those in the skin may simulate nephritis, even to the stage of uremia, or there may exist a severe nephritis, to which the skin lesions are secondary. The skin lesions, needless to say, are exceedingly variable in character, as the variety of names applied to them by dermatologists proves. The synthesis of large numbers of these cases with skin and visceral manifestations into one group, in which various combinations of erythema, hemorrhage, edema, and exudation occur in the skin surfaces and in the viscera, seems more logical than to separate the cases into countless groups depending upon the location of the lesion and its exact features. This was discussed years ago by Osler, and as time has passed and serums have been widely used, it has been found that many cases of so-called serum sickness bear close resemblance to the cases in the erythema class, probably further justifying the grouping of all of these cases, though our knowledge of definite etiology in the erythema group is still very slight. The author reports 10 cases, the symptoms being grouped as follows: Case 1, urticaria, albuminuria, hyperpermealbility of the kidney. Case 2, purpura, abdominal pain, blood in the stools. Case 3, purpura, abdominal pain, pain and swelling of the ankles, hematuria. Case 4, purpura, diarrhea, blood in the stools, abdominal pain, painful, swollen joints. Case 5, purpura, painful joints, hematuria. Case 6, erythema nodosum, abdominal pain, vomiting, slight diarrhea. Case 7, erythema multiforme bullosum, gastric disturbance. Case 8, erythema multiforme vesiculosum, abdominal pain. Case 9, urticaria, intestinal obstruction. Case 10, purpura, arthritis, abdominal pain, hematuria, blood in stools. The study of these cases seems to convince the author that the symptoms are best explained by regarding the disease as due to disturbance in the small bloodvessels (vessels of the capillary, precapillary, and postcapillary group), focal in distribution, which causes dilatation, diapedesis, and exudation either singly or in combination. The ultimate cause is unknown, and the fact that these disturbances occur anywhere within the circulatory system will undeniably result in a large variety of symptoms. That this is so is proved by the extreme variability of the symptoms in any given case. The intestinal colic is the result of changes in the intestinal wall producing spasm, while the diarrhea and blood in the stools probably

result from serous exudation or hemorrhage into the wall of the bowel. The exact relation of the renal changes is not clear. Hematuria can occur from localized changes in the renal vessels, as in the intestine, and this was found to be true in case 10, when the kidneys at autopsy were found to contain numerous focal hemorrhages without a nephritis. In some of the cases study showed a markedly reduced renal function, and in others the question was raised whether or not the renal manifestations were not due to the same changes occurring in the kidney, which occurred in the skin or other tissues. This question is difficult to solve at the present time. It is also possible that the so-called "uremia" occurring occasionally in these cases is due to similar vascular changes in the brain, and is not secondary to the renal lesion. Christian concludes that there is a definite clinical entity, in which skin lesions of the erythema type occur in combination with visceral lesions of the same character. The visceral lesions may occur unaccompanied by skin manifestations, and as the symptomatology within the group is very complex, diagnosis of the visceral lesions may be very difficult in the absence of skin lesions at a given time.

SURGERY

UNDER THE CHARGE OF

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Arterioplasty after Arteriosecretion. — HOFFMANN (*Zentralbl. f. Chir.*, 1916, xliii, 981) says that if after the resection of an aneurysm, a free bleeding occurs from the peripheral cut end of the main arterial trunk, one may depend upon the sufficiency of the collateral circulation after ligation of both stumps. In other, older patients, the collateral circulation is not sufficiently good to rely upon such a procedure, lest the nutrition of the limb below should not be maintained. But there is a certain amount of collateral circulation in every case of aneurysm and one might give sufficient aid to it by conserving a portion of the main arterial current. Hoffmann proceeded as follows in a cases of popliteal aneurysm: After extirpation of the aneurysmal sac which extended downward almost to the bifurcation of the popliteal artery and upward almost the length of this artery; a union of the central with the peripheral cut ends was impossible. The posterior tibial artery was divided just above where it gives off the peroneal artery. The peripheral cut ends here was ligated and the open central end turned upward for circular union with the central cut end of the popliteal artery. The peripheral stump of the popliteal was ligated close to its bifurcation into the anterior and posterior tibial arteries. The lumen of the turned up upper portion of the posterior tibial is seen to be continuous with that of the anterior tibial, and when after dividing obliquely

the open end of the posterior tibial for union with the larger opening in the popliteal artery, these two are united by suture, the arterial current is allowed an uninterrupted course from the popliteal into the anterior tibial through the connecting portion of the posterior tibial. The conservation of the anterior tibial current seems to have been sufficient with the poor collateral circulation, because a good result followed and the patient returned to work.

The Spirochetal Content of the Spinal Fluid of Tabes, General Paresis, and Cerebrospinal Syphilis.—WILE (*Am. Jour. Syph.*, January, 1917, p. 84) says that the question of the spirochetal contents of the spinal fluid is a matter of very great importance not only for the bearing it has on the pathology of the disease, but also from another standpoint. The spinal puncture has today become a routine measure in all well regulated hospitals and is performed, or should be at least at some time during every syphilitic's lifetime. It not infrequently happens in withdrawing the stilette or in collecting the fluid that more or less is spilled over the operator's or attendant's fingers, and in the laboratory the possibility of the fluid being a source of infection is customarily entirely disregarded. If spirochetes are present in spinal fluid the same great care should be used in examination as is employed in the examination of other syphilitic products and secreta. During the past year Wile has inoculated the spinal fluid of eight cases of acute cerebral syphilis, general paresis, and tabes dorsalis, into the rabbit testis. He concludes that the spinal fluid from cases of early syphilis, of tabes and of paresis, contains spirochetes as demonstrated by transplantation into the rabbit testis. The spirochetes may be present in moderate, or even large numbers in the rabbit testis without producing the classic gumma or chancre of the testis. In some cases slight enlargement of the testis itself may be noted. In still others spirochetes were demonstrated in which no increase in size of the testis was noted. In no case in this series were spirochetes demonstrable in the fluid itself before inoculation. The spinal fluid, at least in cases in which the nervous system is involved, must be regarded as infectious, and as such should be handled with the same care as other syphilitic secreta.

The Present Status of Roentgentherapy in the Management of Deepseated Malignancy.—CASE (*Surg., Gynec. and Obst.*, 1917, xxiv, 581) says that the use of the roentgen rays and radium, at least for the present should be restricted to pre- and postoperative irradiation and to the treatment of inoperable malignancies. Radiotherapy does destroy cancer cells. This destruction can be brought about without serious injury to the neighboring normal tissues. The destructive effect is a deep one, both for radium and the roentgen rays. The ideal method is to employ a combination of radium and roentgen therapy in all cases of tumors affecting the cavities of the body. There is no question about the possibility of effecting a local cure of cancer in the human body. We lose our patients in the end because of inaccessible metastases. But in the way of palliation of suffering, prolongation of useful life, and, in a few unexpected cases, clinical cure lasting a decade or longer, there is no known therapeutic agency that can equal the results of radiotherapy.

THERAPEUTICS

UNDER THE CHARGE OF

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The Salicylates.—HANZLIK, SCOTT and THOBURN (*Arch. Int. Med.*, 1917, xix, 1029) note further observations on albuminuria and renal functional changes following the administration of full therapeutic doses of salicylates. They found that the administration of salicylate in full therapeutic doses invariably causes the appearance of albumin, white corpuscles and granular casts or cast-like bodies in the urines of normal rheumatic, non-rheumatic, febrile and afebrile persons. They believe that the albuminuria is not of febrile origin, but due directly to the drug. A preëxisting albuminuria was always aggravated by the administration of salicylate. A diminution of renal functional efficiency was indicated by lessened water excretion, diminished phenolsulphonphthalein excretion and accumulation of urea nitrogen in the blood. They also found that the administration of bicarbonate together with salicylate has practically no demonstrable influence on the albuminuria and renal functional changes produced by the salicylate.

A Simple Method for the Quantitative Determination of Urea in Small Quantities of Blood.—HAHN (*Deutsch. med. Wchnschr.*, 1915, xli, 134) has devised a simple accurate method for the determination of urea in urine and blood, based upon the method of Van Slyke and his co-workers who employed urease to convert urea to ammonian carbonate. The method as applied to urine. In a flask of 50 c.c. capacity one places 1 c.c. of urine, 10 c.c. of water, 2 drops of methyl orange as an indicator, and then titrates immediately with N/10 hydrochloric acid to an orange yellow color (not red) then one adds a small knife point of dry ferment (urease) and 3 drops of toluol and closes the flask with a cork. The next day the fluid in the flask is again titrated with N/10 hydrochloric acid multiplying the number of cubic centimeters of N/10 acid used by 3 mg., giving the amount of urea in 1 c.c. of urine. In determining urea in blood and serous fluids the methyl orange is not a satisfactory indicator. By means of idometry accurate results are obtained. The reagents required are N/100 hydrochloric acid, 5 per cent aqueous solution of thiosylphate, N/100 iodine solution, 1 per cent. starch solution and urease in substance. Method as applied to blood and serous fluids. In an Erlenmeyer flask of 50 c.c. capacity one measures accurately 1 c.c. of serum, adds 20 c.c. of water, a small knife point of the dry ferment and 3 drops of toluol. In a second flask the same mixture is prepared excepting that the ferment is omitted. The two flasks are corked and each allowed to stand at room temperature from eight to twenty hours. Within this time all the urea will have been changed by the ferment in flask 1 to ammonia carbonate. The following operation is then carried through with each flask: One adds 20 c.c. of N/100 hydrochloric acid, shakes well and pours the fluid into a flask

of 150 c.c. capacity, rinses three times with distilled water. Now one adds 0.5 c.c. of the potassium iodide solution and a few granules of potassium iodine. Shake vigorously. The yellow color of the iodine must appear. Next add 20 c.c. of N/100 sodium thiosulphate and 2 c.c. of starch solution. The turbid whitish solution turns green, the end point. The difference in the iodine values for flasks 1 and 11 gives the alkalinity corresponding to the urea present in 1 c.c. of serum. The author adds an excess of N/100 thiosulphate solution and titrates back with iodine solution.

Blood Transfusion in Pernicious Anemia.—ARCHIBALD (*St. Paul Med. Jour.*, 1917, xix, 43) reports 26 cases of pernicious anemia treated by blood transfusion at the Mayo Clinic. A total of 46 transfusions were given to this series of cases. In 15 of the 26 cases, two or more transfusions were necessary. The average hemoglobin percentage in the patients treated was 30 per cent. and the majority of the patients were in an advanced stage of the disease. The interval between transfusions was usually one week. As a rule 500 c.c. of blood were transfused, though one patient who was given only 50 c.c. of blood during a crisis showed a rise of hemoglobin from 24 to 64 per cent. in twenty-three days. Of the entire series, 69 per cent. showed marked and immediate benefit following transfusion. Of 14 unfavorable cases that were considered unsuitable for splenectomy, 50 per cent. were similarly improved. Up to the sixth decade the age of the patient had no bearing on the results. On the other hand, of 5 patients between sixty and seventy years of age but 1 showed definite improvement. Chronic cases with a history of remissions, even though ill for several years, are the most likely to respond to transfusion. Those without remissions often fail to respond. Recent acute cases were usually little influenced. The author says, however, that it is impossible to foretell the results of transfusion in any individual case. He believes that when no benefit is derived from one transfusion, a different donor should be tried. Results following transfusions from relatives were not superior to those in the cases of unrelated donors. The author is of the opinion that when the blood is properly tested transfusion is practically free from danger. Only one patient had a severe reaction; 11 patients had a mild fever for a day or two; 18 of the 26 cases showed a marked rise in hemoglobin, and 12 of these a marked increase in the number of red blood cells. In 9 of the 18 the leukocytes were increased in number, but in no instance was the differential count influenced. General improvement usually paralleled that in the hemoglobin. Distressing numbness, burning and tingling in the hands and feet were relieved by the transfusions.

The Relation of Meninges and Choroid Plexus to Poliomyelitic Infection.—FLEXNER and AMOSS (*Jour. Exper. Med.*, 1917, xxv, 525) say that among the mechanisms which defend the body from infection with the virus of poliomyelitis is the meningeal choroid plexus which normally is capable of excluding the circulating virus from the central nervous organs. The complex plays a part also in preventing infection from virus present on the nasal mucosa. Aseptic fluids which irritate, inflame, or even slightly alter the integrity of the meninges and choroid plexus, diminish or remove their protective function. Normal monkey

or horse serum, isotonic salt solution and Ringer and Locke's solutions, when injected into the meninges, promote infection with the virus of poliomyelitis introduced into the blood, the nose, or the subcutaneous tissues. Simple lumbar puncture and the withdrawal and return of the cerebrospinal fluid in normal monkeys, hemorrhage having been absolutely avoided, do not promote infection with virus injected into the blood; while the replacement of the cerebrospinal fluid of one monkey with that of another does in some instances lead to infection. Simple lumbar puncture attended with even very slight hemorrhage opens the way for the passage of the virus from the blood into the central nervous tissues, and thus promotes infection. Hence, changes in the structure or function of the meningeal choroid plexus complex, too slight to be detected by chemical and cellular changes in the cerebrospinal fluid or by morphological alterations, suffice to diminish in an essential manner its protective powers. Of all the irritant fluids tested by the authors, immune serum alone injected into the meninges is not succeeded by infection from the virus introduced into the blood. The protective property of the immune serum is capable of overcoming the promoting action of normal monkey and horse serum and the other irritants mentioned.

An Antipoliomyelitis Horse Serum.—NEUSTAEDTER and BAUZHOF (*Jour. Am. Med. Assn.*, 1917, lxviii, 1531) make a preliminary report regarding experimental work in protecting monkeys from poliomyelitis infection by the injection of a serum prepared from a horse that had been inoculated first with a preparation presumably containing the poliomyelitis endotoxin and then followed by injections of filtrates containing the germ. The authors found that the serum protected one monkey completely against a rather slowly acting virus. Five neutralization experiments were positive without exception. Other experiments were not so successful; one monkey, injected with two and a half the ordinary fatal dose of a virulent virus, was treated with the serum forty-eight hours after a paralysis was already evident and died with symptoms of bulbar paralysis. The authors state that on account of the scarcity of monkeys, only a few experiments were possible, and so they report the facts without drawing any conclusions. They feel, however, justified in using the serum in human cases especially when human serum is unobtainable.

Remissions in Leukemia Produced by Radium in Cases Completely Resistant to Roentgen Ray and Benzol Treatment.—ORDWAY (*Boston Med. and Surg. Jour.*, clxxvi, 490) says that surface applications of radium in leukemia produce striking, indeed remarkable, improvement in (*a*) the blood-picture which becomes almost normal, (*b*) in the size of the spleen and glands, which are reduced almost to normal, (*c*) in the general condition of the patient, who, from an emaciated and weak condition, may become plump and strong. The duration of remission is variable; it may last from months to years. The results of radium treatment are not regarded as curative. It is believed, however, to be the safest as well as the most prompt palliative measure in cases of chronic leukemia, whether refractory or not to benzol or roentgenotherapy. From the results of radium therapy in leukemia it is believed to be the best form of treatment now at our disposal.

PEDIATRICS

UNDER THE CHARGE OF

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High Calory Feeding in Cases of Typhoid Fever in Children.—
H. H. YERINGTON, M.D. (*California State Jour. Med.*, August, 1917,
vol. xv, No. 8). The writer quotes the diet recommended by several
authors for patients having typhoid fever. All recommended a liquid
diet of low caloric value. High caloric feeding was recommended by
Coleman of New York about ten years ago. The author has used a
modification of the Coleman diet, from 700 to 2500 calories a day in
the form of eggs, broths, lactose, custards and junkets. He claims
that by giving a diet high in fat and carbohydrates and low in protein
weight can be maintained or even increased. He divides the disease
into two stages: (1) the acute or high fever stage; (2) the breaking
temperature and convalescence stage. In the first stage food is not well
taken. In the second stage the calories can be increased rapidly and
the normal weight maintained.

Establishment, Maintenance, and Reinstitution of Breast Feeding.—
J. P. SEDGWICK, M.D. (*Jour. Am. Med. Assn.*, August 11, 1917, vol.
lxix, No. 6). "Persistent demand on the breast is a most important
and continually neglected factor in the establishment, maintenance,
and reinstitution of natural or breast feeding." While the author has
had no personal experience in the establishment of lactation without a
preceding pregnancy he cites the reports of others who have succeeded in
establishing a flow of milk in both the male and female breast by means
of suckling. He says that the premature infant is usually unable to
furnish the physiological sucking instinct necessary to support the
hormones. In his work no attempt is made to put the baby to the breast
at first, but both breasts of the mother are expressed regularly five or
six times a day. He recommends great care in the performance of this
act as follows: "The breast is grasped about 1 or 2 cm. back of the
colored areola, and a milking motion is carried out toward the nipples.
The nurses and the mothers soon gain a manual dexterity which is
surprising. No massage of the breast proper is allowed, as it is of little,
if any, value, and sometimes traumatic, inflammatory reaction. . . .
If our method is intelligently followed, it is possible to keep the mother
of the premature infant from losing her milk." The same method is
recommended not only for maintaining as well as for the reëstablish-
ment of lactation after being interrupted for a greater or less time.

The Technic of Wet-nurse Management in Institutions.—ISAAC A.
ABT, M.D. (*Jour. Am. Med. Assn.*, August 11, 1917, vol. lxix, No. 6).
Breast milk is recommended as the best feeding in infants. In order
to supply this wet-nurses are used. These women are supplied to a
large degree by the maternity hospitals and foundling asylums. The

women are usually glad of an opportunity to remain with their babies. The wet-nurses are selected from women of from twenty to thirty years of age, with babies of three to four weeks, and both baby and mother are subjected to a complete physical examination. In addition the Wassermann test is done on the mother and her vaginal secretions examined for gonococci. An estimate is made of the quantity of lactation by expressing the milk by hand. The foster babies are fed indirectly. The milk is obtained by manual expression, breast pumps being inefficient. This is done every four hours during the day and night. The wer-nurses' own babies are nursed four times during the day, as this stimulates the secretion. If additional food is needed, formulæ are used. Special attention is made to the diet of the wet nurses and to their hours of rest and exercise. The expressed milk is either given at once or as it is needed, being kept in sterile bottles in the refrigerator. The average daily amount secured from each wet-nurse in addition to what she gives her own baby is about thirty-seven ounces.

Problems Connected with the Collection and Production of Human Milk.—B. Raymond Hoobler, M.D. (*Jour. Am. Med. Assn.*, August 11, 1917, vol. lxix, No. 6). The author points out that one of the most important factors in the production of human milk is the diet of the mother. A number of diets were used and the results noted with the following results: "(1) A diet to be efficient must produce a sufficient quantity of milk, containing nutrition adequate to cause an increase in growth of offspring without impairing the tissues of the mother. (2) Diets containing from 2600 to 2900 calories in twenty-four hours produced better results than diets containing from 3400 to 3700 calories. It is of no avail to overfeed in hope of maintaining or increasing the milk supply. (3) Diets containing 2000 calories or less cannot protect maternal tissues and at the same time produce sufficient milk. A nutritive ration of less than 1 : 6 gave best results. (4) Animal protein is better than vegetable protein for purpose of milk production. (5) Nut protein is as efficient as animal protein in elaboration of milk. (6) The best form of animal protein to protect maternal tissues and increase milk production is cow's milk protein."

Acidosis in Infancy and Childhood.—Smith, B.A., M.D. (*Arch. Ped.*, July, 1917, vol. xxxiv, No. 7). The author defines this condition as an abnormal metabolism of carbon leading to the appearance of organic acids in the blood and urine and the formation of ammonia to neutralize these acids. He enumerates the symptoms as follows: "The prodromata are not distinctive and comprise loss of appetite, restlessness, and irritability. The invasion is usually with gastro-intestinal symptoms, vomiting and diarrhea. In three instances the invasion was introduced by bronchial asthma, beginning about twelve hours before the symptoms of intoxication. More often coryza or bronchitis preceded the acidosis by three, four or five days, or even a week. Almost invariably the onset was sudden. Howard feels that recurrent vomiting without demonstrable cause is sufficiently rare to indicate an extremely careful study of apparent causes for various possible predisposing causes. The vomiting is repeated many times and is often propulsive in character. Food is vomited first, then the vomited material changes

quickly to a watery fluid, then mucus, and is either colorless or yellow. In about 25 per cent. of the cases there is a distinct fruity odor to the breath. The tongue is usually heavily coated white or brownish. Thirst is severe. The abdomen is retracted in some of the cases. Constipation is usually obstinate in the severe cases and with this there is marked distention and finally intestinal atony toward the close. In about 25 per cent. of the cases air hunger was present. Cyanosis in a minority of the cases is marked. The pulse is invariably elevated. With high temperature it may go to 160. If the blood is examined it shows the leukoeytes to be from 9000 to 12,000, with a normal differential. The nervous symptoms vary. Infants may be restless, but in the majority, 64 out of 100 cases drowsiness is marked. When aroused the child is fretty and irritable. This may pass on to a condition where it is more and more difficult to arouse the child and finally unconsciousness develops. The reflexes are present and normal. Prostration is marked and the temperature is above 100° F. in the majority of cases. A temperature of 103° and 104° is not uncommon. Of 3 fatal cases 1 had a temperature of 101°, 1 a temperature of 100°, and 1 a temperature of 99.8° F. In the majority of cases there is some evidence of involvement of the respiratory tract, coryza or bronchitis. Respirations are rapid, and in the late stages sighing, and the Cheyne-Stokes type. Dyspnea is pronounced and all the muscles of respiration are brought into play. In very many cases the urine is clear and in about 50 per cent. is scanty in amount. The reaction is acid. The specific gravity varies between 1010 and 1030. In the majority of cases no albumin is found, though in the minority there is a faint trace. In about 90 per cent. of one series of cases acetone was found at first test practically at the beginning of the acute symptoms, which leads to the belief that acidosis of this type is not a sequel of persistent vomiting and starvation. Acetonuria never ceased while the urine was still acid; it tended to persist for several days after the urine became alkaline, especially if the diet were scanty; but in such event the patient showed no toxic symptoms, but if the urine were allowed to revert to former acid conditions, toxic symptoms were likely to recur. Acetonuria was of little moment, then, if alkalinity of urine could be procured." Pneumonia, otitis media and nephritis were complications that were noted. The diagnosis was made on the test of the urine and the symptoms enumerated above.

OBSTETRICS

UNDER THE CHARGE OF

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Puerperal Gangrene of the Extremities.—STEIN (*Surg., Gynec. and Obst.*, October, 1916) contributes an interesting paper upon this subject in which he cites reported cases and contributes two. His first case

was that of a woman, aged twenty years, in apparently good general
health. She was about three months pregnant. The pelvic organs
were apparently normal and it was suspected that the patient had
become infected. Shortly after admission to the hospital a three
months' abortion occurred with foul odor from the fetus and from
the vagina. The next day the temperature became normal but in
the evening rose to 105° F. During the next six days the patient's
temperature varied from 104° to 105° F. without pain and other
symptoms. On the seventh day examination showed numerous gray-
ish white superficial ulcers around the cervix covered with whitish
membrane. Some placental tissue was removed by a curette and
the interior of the uterus was swabbed with tincture of iodin. This
was repeated for the next seven days. The temperature remained
between 101° and 102° F. Seven days after the curetting the patient
complained of pain in the right leg and three days later the right leg
and foot became cold and swollen with bluish discoloration. The
foot was extremely painful to touch and the pulsation of the dorsalis
pedis artery could not be felt. The whole foot became gangrenous.
A line of demarcation formed and amputation had to be done below
the knee. The heart remained normal. Several blood cultures showed
no growth. The Wassermann test was negative. On examining the
amputated tissue there was no thrombus in the anterior tibial or the
dorsal artery of the foot. At the termination of the perineal artery
there was a thrombus in the necrotic muscle and there were thrombi
in the veins. In the literature this is the fourth case on record where
gangrene has followed abortion. In all of the other cases there was
a vegetable endocarditis. The second case was one of labor at full
term in a primipara, aged nineteen years, who was in good general
condition. The Wassermann reaction was negative. Delivery was
effected by a median application of the forceps and laceration repaired
with chromic catgut suture. Two days afterward there was a slight
chill with temperature of 104.5° F. There were ulcerations around
the cervix and in the urine were found albumin and hyaline casts.
The lacerated area sloughed and the tissues were removed. The
patient's fever continued although the heart remained in good condi-
tion. Twelve days after confinement the patient insisted on leaving
the hospital. She returned seven days later or nineteen days after
confinement with a rigid abdomen, temperature 102° to 104° F. and
pulse 110. Both feet were gangrenous about 4 inches above the
ankles and a line of demarcation gradually formed. There was no
pulsation in the femoral arteries. Blood cultures were negative.
The patient's condition did not permit operation and on her death no
autopsy could be obtained. The writer believes that in the second
case the thrombus from the uterus passed through the uterine artery
and thence into the circulation to the bifurcation of the aorta and
occluded both iliacs, thus causing gangrene on both sides. In the
first case after abortion it is thought that the venous obstruction
occurred first and that the artery became later occluded. The writer
has collected cases from the literature of gangrene after childbirth
abortion, during pregnancy and after gynecological operations. He
adds a case contributed by Lilienthal, of New York. This patient,
aged twenty-eight years, thirteen years previously had an abortion

followed by septic infection. She had subsequently been operated upon for dysmenorrhea and four months before entering the hospital the appendix and right ovary had been removed and ventral suspension had been performed. An exploration of the upper abdomen was made at this time. Ten days after this operation there was sudden pain and tingling in the ends of the fingers of the left hand. Two days later dry gangrene of the fingers and end of the thumb developed. The patient had lost weight and when admitted to the hospital was in a much depressed condition. She had severe gastric symptoms and there was stomatitis and vaginitis which gradually disappeared with cleanliness. All four fingers of the left hand were practically mumified. The urine was normal. There was no pulse in the left radial artery and none in the brachial until near the axillary where feeble pulsations could be made out. The heart sounds were normal. Blood-pressure was 87 and 114. Under nitrous oxide and oxygen anesthesia the fingers were amputated and several spurting vessels had to be tied. No flap operation was made and the thumb was not operated upon. Wassermann test showed $+ +$ reaction. The patient grew steadily worse and the roentgen ray showed obstruction in the upper part of the jejunum. Entero-enterostomy was performed and vomiting ceased. The patient gradually failed and died. There were no signs of peritonitis. At autopsy there was a patch the size of a quarter of a dollar in the aorta close to the ventricle and adherent to this was an organized clot, part of which had undoubtedly broken off and clogged the brachial artery. On examination aortitis was present and in view of the positive Wassermann findings syphilis suggested itself as the possible cause. In 53 of the cases the lower extremities were both affected fifteen times; the left, sixteen; the right, fifteen. In 1 case both hands, both feet, the tip of the nose and portions of the ears were gangrenous. In 2 cases there was gangrene of an arm and a leg. After abortion there were 3 cases of gangrene of the lower extremities and 1 in which both were affected. Gangrene in the upper extremities in puerperal cases is comparatively rare as but 10 cases are reported. After gynecological operations but 5 cases were collected. These had all been abdominal sections. In most of the cases some lesion of the heart or vessels was present and very rarely a patent foramen ovale seemed to be the cause. Typhoid fever, pneumonia and pleurisy preceded gangrene in some cases. Puerperal fever and obliterative endarteritis were present in 1 case and severe puerperal sepsis treated by abdominal hysterectomy was present in another. General septic infection occurred but rarely and pyemia but once. In 6 cases gangrene complicated eclampsia and in 2 puerperal mania. Some of the cases occurred suddenly and without known cause and there seemed to be no connection between the general health of the patient, the type of labor and the occurrence of gangrene. So far as prevention is concerned whatever brings the patient into good general condition at the time of labor is certainly indicated. Aseptic precautions for the patient and antiseptic precautions for doctors and nurses are imperative. At labor hemorrhage should be prevented and the circulation disturbed as little as possible during obstetrical operations. When the condition develops and the patient is sufficiently strong to endure the operation, amputation must be promptly performed.

OTOLOGY

UNDER THE CHARGE OF

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Lesions of the Middle Ear of Aerial Causation.—TAUPIQUET (*Rev. de Laryngol., Otol. et de Rhinol.*, December, 1916). In a large number of cases of injury of the ear, from proximate shell explosions, the number of instances of implication of the internal ear was small. Of 164 cases in one group, for instances, only 26 were instances of concussion of the labyrinth with or without lesion of the middle ear. The cases of injury to the middle ear, without labyrinthine complication the author divides into three classes: those in which a purulent otitis media is the immediate sequence of the injury with a destruction so extensive as to obviate the possibility of differentiation in degree; those in which there was evident a fresh perforation or extensive rupture of the drumhead with free bleeding, tendency to coaptation of the irregular edges of the ruptures and spontaneous healing, without middle ear infection, in cases of infection, however, this evidenced itself usually within the first two or three days. Of the 24 cases of this class 18 were infected. In the third class of cases, 32 in number, the lesion evidenced on objective examination was not a perforation but a condition, similar to that sometimes found in aviators, of varying degrees of intratympanic or intramembranous hemorrhage with occasional hemorrhagic bullæ, usually in the upper quadrants or at the level of the pars flaccida. These hemorrhagic lesions gradually disappeared and within a few days the drum-head was again normal, unless the strain and injury to the implicated tissue had been sufficient to cause necrosis and perforation. This secondary result occurred in 20 of the 32 cases in this class, the time of its appearance being from three or four days to a fortnight after the injury, the appearance of the perforation, circular or lenticular in shape and with rounded edges, differentiating it from the primary rupture or tear across the drum-head usually posterior to and following the long axis of the malleus.

Shell Explosion Deafness.—RAUJARD (*Bull. de l'Acad. de méd.*, Paris, September, 1916). In this contribution to the study of the varied results of auditory implication from shell fire, the author differentiates between the organic and neuropathic cases without reference to middle ear participation, regarding as organic those cases in which the organ of Corti is really injured and as neuropathic those in which the auditory function is merely inhibited. In the organic form there is, either with or without otitis media, evidence of labyrinth concussion or auditory neuritis, while the true neuropathic deafness is usually accompanied by mutism, is bilateral and complete for all sounds and is not accompanied by evidences of vestibular disturbance, but since these symptoms may occur in some cases of organic deafness the

differential diagnosis cannot always be immediately made. and the elements of time and the effects of psychotherapy and of reëducation must come into consideration. In this connection the observations of Lannois and of Chavanne are of interest. who reported, in the *Lyon Méd.* of February, 1916, the examination of 1000 soldiers, in 645 apparently total, or nearly total, deafness dated from an aerial concussion, without direct traumatism, all but 2 per cent. recovered, and these were left permanently deaf in both ears.

Method of Closing Post-aural Fistula. — As an example of his method L. J. Curtin (*Jour. Laryngol., Rhinol., and Otol.,* February, 1917) reports the case of a boy, aged eleven years, with a persistent mastoid fistula, the sequence of a simple mastoid operation two years previously. The author did a radical operation with a resultant re-opening of the fistula, the closure of which was effected by refreshment of the fistulous edges and a linear reunion of the wound, avoidance of tension upon the suture being accomplished by means of a new vertical linear incision, three-fourths of an inch behind that for the immediate closure of the radical mastoid wound, a thin elevator being used for dissection of the periosteum of the resultant flap, which it was therefore possible to slip forward and suture without strain upon the edges of the anterior incision; the further postaural gap in the skin of the scalp was then filled by a skin graft from the inner side of the arm. The result in this case was healing of the radical mastoid wound by first intention and consequent obliteration of the fistulous opening a result similar to that which would have been obtainable by a still further postaural periosteal dissection and a slipping of the scalp forward for closure of the secondary opening as a substitute for the closure by the flap operaton, as has been effected, in like cases, by other surgeons.

War Injuries, Auricle and External Meatus. — Marriage and Cheatte (*Jour. Laryngol., Rhinol. and Otol.,* June, 1917). Wounds from an individual missile or from personal contact in hand-to-hand fighting vary greatly in character and in extent, the auricle may be pierced by a bullet, shredded by small pieces of rental which have passed through or remain lodged in it or it may have been almost torn away. In dealing with these cases all that is usually required is cleansing the wound, removing imbedded metal and applying antiseptic dressing, it being often possible to save a large part of the auricle by plastic operation, the chief complication being necrosis of the cartilage. Wounds of the cartilaginous portion of the canal were usually caused by missiles entering from in front or behind with or without implication of the bony canal; in one instance a bullet entered in front of the tragus; passed through the cartilaginous canal, striking the tip of the mastoid causing a slight fracture, as shown by the *x*-ray examination and emerging below; the wound of exit was about the size of a hazel-nut and fitted in without involvement of the mastoid. The drum-head was not injured, but there was some impairment of hearing referable to the labyrinth as a result of the concussion. Mr. Arthur Cheatte reports 2 cases, 1 in which a nearly spent machine-gun bullet entered the right meatus, passing through the cartilaginous canal without injury, striking and penetrating the anterior bony wall being then

deflected downward and backward and emerging behind the upper third of the sternomastoid, lodged in the collar badge, the soldier was knocked down without losing consciousness and was dazed, giddy, and sick. When seen, a few days later, there was a slight thin discharge from the ear, the cartilaginous canal was normal, but the anterior and inferior walls of the bony canal were swollen and there was a granulation obscuring the anterior half of the drum-head, there was also a healing wound one and a half inches in length behind the sternomastoid in its upper third. The patient complained of deafness and subjective noises, difficulty and pain on moving the jaw; there was no bony crepitus, but distinct synovial creaking. The voice in conversation tone was heard at a distance of six feet and the tuning-fork by bone conduction was heard in the affected ear. There was neither pain, dizziness, nystagmus nor facial paralysis. A few days later the slight discharge became offensive and facial paralysis gradually developed, but after saline syringing for a few weeks the discharge ceased and the paralysis disappeared. Examination of the drum-head which was then possible showed that it has been ruptured in the anterior inferior segment, the hearing subsequently became nearly normal. The second case was that of a lieutenant who, while looking through field glasses, was struck by a rifle bullet fired from a range of less than three hundred yards, which passed through the palm of the left hand, glanced off the malar bone and passed through the meatus cutting the auricle in half, he was unconscious for a few minutes and, on recovery, dizzy and nauseated, and had a facial paralysis which persisted for about two months. Six weeks after the injury the wounds were healed but there was complete cicatricial closure of the meatus. For five weeks after the injury he had disturbance of equilibrium and much unsteadiness in walking and had not been able to hear in the affected ear. The examination made two months after the injury showed the hearing to be absolutely wanting in the left ear either aerially or by bone conduction and there was no nystagmus on rotation.

Contribution to the Etiology and Pathogenesis of Otogenic Sinus Phlebitis.—(*Journal of Laryngol., Rhinol., and Otol.*, vol. xxxi, No. 12). —In this paper, based upon the observation of 20 cases of otogenic sinus phlebitis operated upon by the author and statistically reported, it is concluded that the jugular bulb is the most frequent place for the inception of otogenic thrombophlebitis, the fact being that in 16 out of 53 cases in which a clot was found in the sigmoid sinus, no bleeding could be produced by applying the sharp spoon in the direction of the bulb because there was a clot there, while profuse bleeding resulted from the application of the sharp spoon in the opposite direction. In this respect the author supports Jansen in his opinion that the jugular bulb plays an important part as the place of origin of thrombophlebitis, but disagrees with the latter writer in the opinion that this applies only to thrombophlebitis caused by acute middle ear inflammation. The majority of the author's cases, where the jugular bulb probably or certainly was the primary place of origin, were cases of chronic middle ear suppuration frequently accompanied by cholesteatomatous accumulation. In the author's opinion the otogenic sepsis is a pathogenic unity which, perhaps with a few exceptions, is caused by a thrombophlebitis of the sigmoid sinus or of the bulb or of both united.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Experimental Observations on the Pathogenesis of Gall-bladder Infections in Typhoid, Cholera and Dysentery.—Starting with the well-known fact that the chronic carrier of organisms of the typhoid group became such only as the result of infection which in the majority of cases is localized in the gall-bladder, NICHOLAS (*Jour. Exper. Med.*, 1916, xxi, 497) reports a series of animal experiments designed to prove the descending route of infection of the gall-bladder by organisms filtered from the blood by the liver and secreted in the bile. The writer states that the ascending route is scarcely to be considered, while the work of Koch and Chiarolanza (1908) which has led to the acceptance of the direct infection from the blood through the gall-bladder wall as the usual mode of infection must be discredited. Koch drew his conclusions from the histological picture in human typhoid cholecystitis, by demonstrating bacillary emboli in the mucosal lining. Chiarolanza tied the cystic duct and immediately injected typhoid bacilli, later recovering the organisms from the gall-bladder. Doerr, it is pointed out, had performed the same experiment more correctly in 1905. His injection of bacilli was not made until several days after the ligation of the cystic duct. This eliminated the initial hemorrhage incident to the ligation, which Nichols is convinced gave Chiarolanza a dilute blood culture with positive results in the bile, inasmuch as Doerr obtained negative results by waiting several days before making the intravenous injection. In developing his thesis, the two main conditions to be met are, first, that the bacilli may get into the bile, and second that they may be able to multiply there. To demonstrate the first point, a common duct fistula was devised, using a capillary glass cannula with a slender rubber tube leading to the exterior where a sterile receptacle was attached to collect the bile. Then, employing both subcutaneous and intravenous injections of bacilli, the experimenter determined that the organisms appeared in the bile after short intervals. While bacteria may be obtained, true lesions of the gall-bladder occur in only 50 per cent. of injected animals, and the author believed that if an explanation of the failure of the intravenous injection to produce 100 per cent. of lesions could be found, it might furnish a clue to the whole problem. The relation of gall-bladder lesions to the number of bacilli in the bile was investigated, having first demonstrated by actual count of the colonies

in plated specimens of bile that the number of bacteria could be influenced by the site of injection. It was found that injection of the mesenteric veins gave more organisms in the specimens of bile subsequently obtained, while the gall-bladders of these animals showed more frequent lesions. An interesting point also brought out in this connection is that animals immunized against the type of organism injected showed more bacilli in the bile, while the incidence of gall-bladder lesions was also higher. This indicates a high immunity with the bacteria freely eliminated by the liver as a result of an agglutinative process. The type of lesion produced in the gall-bladder is not discussed by the author. Having demonstrated the ability of the organisms to enter the bile and gall-bladder by the descending route, as a result of a filtration action of the liver, the author next turns to the subject of the antiseptic properties of the bile, and presents a number of interesting facts. Among others, he quotes Okada to the effect that the bile from the gall-bladder is less alkaline and contains more solids than that in the liver. Also, that healthy bile may have a distinctly bactericidal action on the typhoid bacillus, though it has been used as a culture medium for this organism. And finally, that rabbit and especially guinea-pig bile have a very high bactericidal power. Here is noted the fact, too often not realized, of the differences between man and the experimental animals. The reactions of various types of bile, including that from the ox, the human, from rabbits and from guinea-pigs, show a wide variation. The highest alkalinity by far is found in the guinea-pig, with the rabbit next in order. This seems to point to alkalinity as the source of the bactericidal power, especially since neutralization of the alkalinity was found to reduce this power. This brings the author to a discussion of the question of prophylaxis in the diseases under consideration, with a view to preventing gall-bladder infections and hence, carriers. This subject he treats conservatively, advising against the employment of what is really experimental treatment on a patient already suffering from a severe acute infection, though if a mild therapy were of value, he feels it to be justified. He adds that though alkaline treatment in cholera is useful to combat uremia, it might not be as useful in this as in the other infections since the cholera vibrio flourishes in an alkaline medium. However, after recovery from an acute attack of one of these diseases, the patient should not be discharged as cured until the possibility of his being a carrier has been eliminated. For this, in addition to examination of the stool, the writer believes that Einhorn's duodenal tube should be of value. Here it may be stated that Garbat has recently reported the successful application of this method for the determination of carriers among the convalescent typhoid patients in a New York Hospital.

Hyaline Degeneration of the Arteries.—The study of the lesions occurring in human arteries is still in the stage of the collecting of facts and has not yet arrived at the time for setting up broad principles. Each independent study assists in elucidating particular points concerning the nature and origin of pathological processes in arteries. Too many attempts have been made in the earlier stages of arterial study to formulate laws concerning all the processes associated with arteriosclerosis. At the present time, very few of these theories are

supported, and investigations have shown that there are so many underlying conditions and active causative factors that we cannot hope for the discovery of one law but that with the variety of arterial lesions many principles of pathology will be found involved. JACOB (*Jour. Med. Res.*, 1916, xxxv, 187) has studied the occurrence of hyaline in various portions of the arterial coat. He found that its first appearance is in the spleen and ovaries in which it may be found after the age of fifteen years. In one instance this product of degeneration occurred in the spleen of a child of three years, dying from empyema. In other cases he has also observed the bearing of acute infective diseases upon the deposit of hyaline. In the kidney hyaline appears more frequently about the capillaries of the glomeruli following various grades of renal inflammation. In the later stages of the kidney affection the larger arteries also show hyaline degeneration occupying the middle coat of their walls. In the large arteries hyaline appears with greater frequency with advancing age and here it is to be looked upon as the evidence of many insults brought to bear upon the arterial coats. The importance of the presence of hyaline does not lie in the immediate effect upon the arterial wall but in the variety of circumstances which have brought it about. Under some conditions the hyaline deposit represents a process of degeneration secondary to a tissue reaction of a proliferative kind. This is particularly true in the appearance of hyaline in the nodular thickenings of the intima of the aorta. On the other hand the development of band-like deposits of hyaline in the deep portions of the intima suggests a tissue response resulting from a systemic process. No clear light has been thrown upon the manner in which this form of hyaline is laid down. The author points out that this type of hyaline has much in common with an amyloid deposit.

Spontaneous Infection in the Guinea-pig.—The guinea-pig is probably the most commonly used animal for laboratory experimentation. This being true makes it essential that the experimenter should be familiar with the spontaneous disease affecting this animal to avoid confusion and wrong deductions from his experiment. It has not been uncommonly found that, in carrying out bacteriological problems necessitating the use of animals for studying pathogenicity or immune reactions, confusion has arisen due to the presence of microörganisms in the animal tissues not used in the experiment. These laboratory animals harbor a bacterial flora which remains fairly constant under normal conditions. Where, however, the animal suffers from spontaneous disease or is made the subject of experiment, an invasion of these bacteria may take place into tissues usually found sterile. HOLMAN (*Jour. Med. Res.*, 1916, xxxv, 151) has made a bacteriological investigation of 200 guinea-pigs dead of spontaneous infection. The types of microörganisms isolated from these animals as well as the localization and distribution in the tissues is taken up in this study. The author points out the great variety of bacteria which may spontaneously infect the guinea-pig. A thorough review of the literature makes the work valuable for those using the guinea-pig in experiments in bacteriology. The finding of various members of the streptococci as having a pathogenicity for this animal and showing high invasive qualities under conditions of disease, has an important bearing upon the use of the guinea-

pig in studies upon this microörganism. The ease with which a misinterpretation upon the transmutation of organisms within the living body may occur, is demonstrated in the finding that the inoculation of one type of streptococcus may lead to the invasion by other types from natural foci in the animal. More striking is the fact that widely different types of bacteria may lead to lesions in the animal permitting of spontaneous secondary infection and mixed cultures. It is also pointed out that particular regions and laboratories have outbreaks of epidemics more or less peculiar to the locality. This has been illustrated in the epidemics of pneumococcus infection in several laboratories, a type of infection not met with by the author. The author also drawn attention to the frequency of acute and chronic pneumonia in guinea-pigs from infections by the B. bronchisepticus.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Laboratory Infection Caused by a Bovine Strain of Bacillus Enteritidis.—MEYER (*Jour. Infect. Dis.*, November, 1916, vol. xix, No. 5, pp. 700–707) presents clinical, bacteriological, and serological observations of an accidental laboratory infection. A young man who apparently was predisposed to the infection on account of a chronic mucous colitis developed a severe gastro-enteritis ten hours after having handled a bottle of sterilized milk which was artificially contaminated with a culture of B. enteritidis (Gärtner). The strain responsible for the infection had been isolated from the heart blood of a calf which had succumbed to infectious diarrhea. Evidence is presented to show that a recently isolated strain of B. enteritidis pathogenic for animals may differ from a strain pathogenic for man in its inability to be coagglutinated by paratyphoid or suipestifer sera.

Immune Reactions in Scarlet Fever.—G. F. and G. R. DICK (*Jour. Infect. Dis.*, October, 1916, vol. xix, No. 4) in a previous work, reported a weakly positive reaction in a complement-fixation test using mucus from scarlatinal angina as antigen. On the supposition that the antigenic property of the mucus was due to microörganisms capable of growth, cultures were made of the mucus and tested as to antigenic properties by complement fixation and intracutaneous reactions. In the complement-fixation tests the antigen was prepared by inoculating milk with mucus from a scarlatinal throat, and a control antigen was made from

the throat of a case of Ludwig's angina. The cultures from scarlatinal throats showed the presence of an antigen which reacted with scarlatinal serum to fix complement in more than one-half the case tested, whereas the control antigen from Ludwig's angina gave positive reactions in over one-third of the cases tested. Three other antigens were prepared by making a broth-mucus mixture and incubating one antigen twenty-four hours, one forty-eight hours, and one not at all. Using these, it was found that the antigen with twenty-four hours' incubation gave the best results, thus establishing the incubation period of the antigen present in the cultures as twenty-four hours. Examinations of the six antigens used showed the predominant growth to be streptococci, so in order to compare the antigenic property of streptococci with that of the mixed cultures an antigen was made using a hemolytic streptococcus isolated from scarlatinal angina. Tests were carried out in nine cases of scarlatina, and 88 per cent. of these showed fixation of complement. In order to compare the antigenic property of streptococci with that of other organisms from scaralatinal anginas, antigens were made from a number of organisms isolated in pure culture from cases. It was found that the only organisms tested which appeared to produce immune bodies in scarlatina with any degree of constancy was the streptococcus. Cutaneous tests on convalescent scarlet fever patients were carried out with the antigens used for the complement-fixation tests, and, as controls, diphtheria patients who gave no history of scarlet fever were injected. The technic used was similar to that of the intracutaneous tuberculin, and Schick tests and the antigen was a heat-sterilized culture of mucus from scarlatinal angina. In 12 scarlet fever patients there developed at the site of injection areas of reddening and induration which reached a maximum on the day following the injection and then gradually disappeared. The reactions in the controls were much less marked.

Bacteriological Studies on Experimental Scurvy in Guinea-pigs.— Jackson and Moody (*Jour. Infect. Dis.*, September, 1916, vol. xix, No. 3) undertook this work primarly to determine whether certain small stained bodies seen in sections of scurvy lesions were bacteria. In the investigation of diseases in laboratory animals affecting chiefly the skeletal system, some authors have ascribed to them an infectious origin. Experimental scurvy was produced in guinea-pigs and cultures made from the diseased tissues. From such cultures was isolated a diplococcus showing a tendency to form chains and to produce green colonies on blood agar. Pure strains of these microörganisms inoculated into the circulation of normal guinea-pigs gave rise in most cases to hemorrhagic and other lesions in the bones, joints, and muscles, lymph glands or gums. From these lesions were recovered streptococci of the same type as those injected, and bacteria resembling these organisms were frequently seen in the microscopic sections of the scurvy lesions. Cultures of the heart blood from the scorbutic guinea-pigs were sterile, and blood from these animals failed to produce the disease in a normal pig. In guinea-pigs which had artificially received these streptococci in their circulation, but had their resistance kept high by proper feeding, the lesions produced did not have the same tendency to progress that was seen in animals receiving an unbalanced diet.

A Tuberculosis Survey of an Alaskan Eskimo Village.—MICHIE (*Med. Rec.*, October 14, 1916, vol. xc, No. 16) considers the Eskimo is predisposed to tuberculosis from every aspect. The housing and living condition among these people are most unsanitary and their food is very bad, consisting principally of uncooked fish, seal meat and oil. As a result of this unfavorable environment, any communicable disease spreads rapidly among the Eskimos; their resistance is very low and they are easy prey for epidemics. A tuberculosis survey of the children under fifteen years of age in one of Alaska's cleanest villages was made. The von Pirquet tuberculin test (using Koch's O. T.) was made on the children in the two schools at St. Michael. Of 24 children examined, more than 61.5 per cent. were tuberculous. There were also several suspicious cases which would probably have proved positive if several examinations had been made. The author concludes by saying that the Eskimo's entire system of living is wrong, but that on account of ignorance, superstition, and climatic conditions the only relief measure practicable at the present time is the enactment of the necessary legislation to prevent traders from robbing the Eskimos and to grant larger medical appropriation for use in Alaska.

Miner's Consumption.—LANZA (*Public Health Bulletin*, No. 85, January, 1917) made a study of 234 cases of miner's consumption among zinc miners in western Missouri, and concludes that it is an important occupational disease, widely prevalent among the hard-rock miners of the Joplin district, affecting probably 30 to 35 per cent. of them. It is essentially a pneumonoconiosis, due to the inhalation of silicious rock dust, and resulting in a fibrosis, with loss of function. The disability and other effects of miner's consumption are due primarily to silicosis, infection being usually a secondary, and often a terminal process. Infection, both tuberculous and pyogenic, is common, the tendency to infectioo increasing as the disease progresses. The incidence of tubercle infection in miner's consumption is a menace to the public health, affording an unusual opportunity for the spread of tuberculosis. Aside from the hygienic supervision of working conditions underground education of the miner against the spread of infection and supervision of miners' children, especially those of consumptive parents, are matters of vital importance.

The Therapeutic Value of Pertussis Vaccine in Whooping Cough.—Referring to the favorable reports of LUTTINGER (*Jour. Am. Med. Assn.*, May 19, 1917, lxviii, pp. 1461–1464) abstracted in the September number of this JOURNAL, it is important to consider the results of VON SHOLLY, BLUM and SMITH (*Jour. Am. Med. Assn.*, May 19, 1917, lxviii, pp. 1451–1456), who are more conservative in their conclusions, and believe that more observations and more critical observations with controls for comparison must be made before the case can be considered made out for the curative and prophylactic value of a specific pertussis vaccine. Von Sholly, Blum and Smith give the following summary: Since whooping cough vaccine statistics under present conditions must be based chiefly on parents' reports, one must use careful

judgment in accepting what they say. Statistics to be of any value must be drawn from several thousand cases, as shown by the variable results obtained with different groupings of figures. One must be aware of "impressions." Figures show that the non-specific influenza vaccine differs very little from pertussis vaccine in influencing the duration of the paroxysmal stages of the disease. In a second group it shortens the average length of this stage by eight days. In the third group it acts less well, on the whole, than the specific vaccine in the mild cases, and better than the specific vaccine in the moderate and severe cases. Of all the cases, the shortest course was run in our non-vaccinated controls and those receiving inert, milk-colored water. None of the patients inoculated for prophylaxis with either influenza or pertussis vaccine contracted the disease. A partial immunity was exhibited by 31.6 per cent. of the families studied; 58 per cent. of the children in these partially immune families escaped after exposure in the family. Of 700 children exposed in their families, 24.9 per cent. escaped whooping cough.

Diphtheria Bacilli in Microscopic Sections of Tonsils from Diphtheria Carriers.—BROWN (*Jour. Infect. Dis.*, October, 1916, vol. xix, No. 4) sectioned the tonsils of diphtheria carriers to study the presence and location of diphtheria bacilli. This work was done as a result of the report of Friedberg, Ruh, Miller, and Perkins that certain persistent diphtheria carriers gave negative cultures after tonsillectomy and removal of adenoids. The tonsils studied were from 7 diphtheria carriers, all of which had had positive cultures from nose or throat for twenty-one days or over. Tonsils from 14 patients who had undergone tonsillectomy for various other causes were used as controls. The tonsils were fixed in a solution of equal parts of absolute alcohol and bichloride of mercury, run through paraffin, cut and stained by the Gram-Weigert method. Of the 7 diphtheria carriers, 6 showed Gram-positive headed bacilli in large numbers. These were found chiefly in the crypts in the plugs of tissue and in the tissues lining the crypts in which the epithelium was very thin. One case showed no Gram-positive bacilli and yet gave positive cultures from the throat for four days and from the nose for nineteen days after tonsillectomy and removal of adenoids. Probably in this case, the bacteria were multiplying in some other place. Of the 14 pairs of control tonsils studied only 2 showed any Gram-positive bacilli. The author draws the conclusion that the cleaning up of diphtheria carrier cases by tonsillectomy is due to the removal of an important focus of infection in which the bacilli lodged and multiplied.

ORIGINAL ARTICLES

THE COMPARATIVE VALUE OF THE WASSERMANN, THE COLLOIDAL GOLD AND OTHER SPINAL FLUID TESTS: A STUDY OF 203 CASES.[1]

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Both clinical studies and laboratory investigations, especially in the past few years, have increased our diagnostic ability in organic nervous diseases to a marked degree. New methods and tests have been added in rapid succession. Since the introduction of the lumbar puncture by Quincke, in 1891, the examination of the spinal fluid has become more and more frequent, and at the present time no neurologist has scientifically completed his study of a doubtful neurological case unless he has made a thorough and comprehensive study of the spinal fluid.

The routine study of the spinal fluid comprises a cell count, a globulin test, a Fehling test, a Wassermann, a colloidal gold test and an examination for bacteria when indicated. In our work Dr. Riggs, Dr. Michael and myself have followed this routine examination as closely as possible in order to estimate the comparative value of the various tests in syphilitic and non-syphilitic diseases of the central nervous system. The cell count was made in the Fuchs-Rosenthal counting chamber and a diluting fluid containing methyl violet was used.

[1] Thesis, read before the Minnesota Academy of Medicine, October 11, 1916.

In testing for increased globulin we used:

(a) *The Nonne Test.* By adding equal parts of spinal fluid with a neutral hot saturated solution of ammonium sulphate. Cloudiness within three minutes means a positive test.

(b) *Noguchi Test.* Take one part spinal fluid, add 4 parts 10 per cent. butyric acid, let come to a boil, add one part normal NaOH, let come to a boil. A positive test gives a flocculent precipitate within one-half hour.

(c) *Pandy's Test.* Take from 0.5 to 1 c.c. of a saturated aqueous solution of carbolic acid and add to it one drop of spinal fluid. The immediate formation of a bluish-white ring or cloud means an increased amount of globulin in the spinal fluid. For the most part these three reactions have been parallel. I personally prefer the Noguchi test, probably because I have used it more frequently than the others.

The Fehling Test. The Fehling test did not reveal anything of diagnostic value. It was positive in practically all cases.

The Colloidal Gold Test. This test was first introduced by Lange in 1912. Its principle depends upon the protective action of certain colloids, especially proteins, on the precipitation of gold suspensions by sodium chloride. Lange found that a 0.4 per cent. pure sodium chloride solution was of sufficient strength to keep the normal spinal fluid proteins in solution, but too weak to cause flocculation of colloidal gold solutions. In abnormal spinal fluids, on account of their high protein content, one naturally expected a greater degree of protection. However, this was not the case, and Lange observed that partial or complete precipitation of colloidal gold with resultant color changes was produced by these fluids with almost definite curves, especially from those spinal fluids of luetic origin. Fluids from tabes and cerebrospinal lues gave their maximal reactions in the lower dilutions, and this change has been so constant that it is spoken of as the "luetic zone" and "luetic curve;" fluids from the different types of meningitis gave reactions with their greatest intensity in the higher dilutions, commonly known as "Verschiebung nach oben;" fluids from paretics caused complete flocculation in the first four to six tubes with such regularity that Miller and Levy suggested the term "paretic curve." In Lange's original conclusions he states that normal cerebrospinal fluid produces no color changes in any dilution in the colloidal gold solution. Most workers, however, believe that slight color changes up to a purple color can occur in an absolutely normal spinal fluid. The colloidal gold test is very simple to perform, is readily interpreted, and requires only 0.2 c.c. cerebrospinal fluid. However, the preparation of the colloidal gold solution is most difficult. Frequently an apparently excellent solution is worthless. Miller and his co-workers have adopted the following standards:

1. The solution must be absolutely transparent and preferably of a brilliant red-orange or salmon-red color.

2. Five c.c. of the solution must be completely precipitated by 1.7 c.c. of a 1 per cent. sodium chloride solution in the time interval of one hour.

3. The solution must be neutral in reaction on the day on which it is used.

4. It must give a typical reaction curve with a known paretic cerebrospinal fluid.

5. It must produce no reaction greater than a No. 1, with a known cerebrospinal fluid.

It frequently requires four or five attempts before a satisfactory solution is procured. The colloidal gold solution may be prepared in three different ways:

Lange's Method. Take 1000 c.c. of fresh doubly distilled water, add 10 c.c. of a 1 per cent. Merck's gold chloride solution and 10 c.c. of a 2 per cent. solution of K_2CO_3. Heat rapidly to the boiling-point, stir vigorously, and add 10 c.c. of a 1 per cent. solution of formalin. The colorless solution must at once assume a clear port-wine color.

Eike's Method. Take 1000 c.c. of fresh doubly distilled water, add 10 c.c. of a 1 per cent. solution of Merck's gold chloride and 5 c.c. of a 5 per cent. dextrose solution. Heat to 90° to 95° and then add a 5 per cent. solution of K_2CO_3, one drop at a time, until the required color is secured.

Oetiker's Modification of Eike's Method. Oetiker believed that the failures in procuring proper solution were due to two factors: (1) the variation in temperature, and (2) the variable amount of alkali solution added. He uses Eike's method; heats the solution to exactly 90° and without turning off the flame adds at once 12 c.c. of a 2 per cent. K_2CO_3 solution. With this method he has had no difficulty in getting satisfactory solutions. We have used most frequently Lange's method and of late Oetiker's modification of Eike's method; the latter is very satisfactory. The test is made as follows: Take eleven small test-tubes, carefully cleaned. In the first one put 1.8 c.c. of a fresh sterile 0.4 per cent. NaCL solution. In the remaining ten tubes put 1 c.c. of the same sodium chloride solution. To the first tube add 0.2 c.c. of the spinal fluid to be tested, making a dilution of 1 to 10. Mix thoroughly and transfer 1 c.c. from tube 1 to tube 2, again mix thoroughly and transfer 1 c.c. from tube 2 to tube 3, continue this process up to and including the tenth tube. This gives a series of dilutions ranging from 1 to 10 in tube 1 to 1 to 5120 in tube 10. Now add to each of the eleven tubes 5 c.c. of a satisfactory colloidal gold solution. Shake thoroughly and make readings in one-half hour and again in twenty-four hours. There is rarely any difference except of intensity between the half-hour and twenty-four-hour reading. The readings

are tabulated in numericals from 0 to 5 : 0 meaning no color change; 1 a red blue; 2 a purple; 3 a blue; 4 a pale blue; 5 a complete decolorization.

The four typical curves are demonstrated in the following table:

☆ COLOR REACTIONS	DILUTIONS									
	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120
COMPLETE DECOLORATION 5										
PALE BLUE 4										
BLUE 3										
PURPLE 2										
RED BLUE 1										
PORTWINE RED 0										
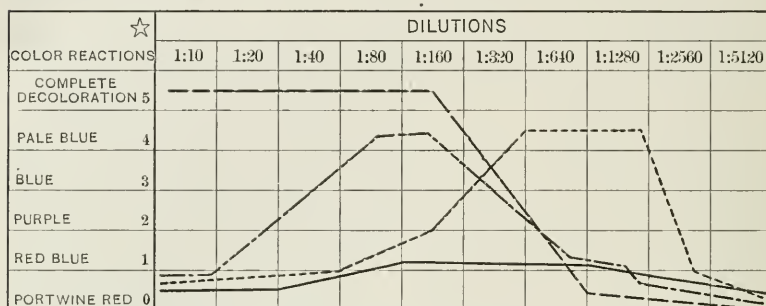
——— No or slight change. Normal spinal fluid.
. . . . Meningitic curve or "Verschiebung nach oben."
–.–.– Leutic curve.
– – – Paretic curve.
Chart taken from article reference No. 16.

According to Lange the presence of blood in the spinal fluid causes color changes in the first four tubes. This is very important, for occasionally one procures a bloody spinal fluid, due to the lumbar puncture. We have repeatedly tested spinal fluids containing blood, either accidentally or added directly, in order to determine this point. Very small amounts of blood caused absolutely no change in the colloidal gold curve different from that produced by spinal fluid alone. However, when enough blood was present to make the spinal fluid distinctly hemorrhagic there was a marked color change in the first four to six tubes. This is in accord with Oetiker's observations. If a spinal fluid is kept sterile, age has no effect on the colloidal gold test. Oetiker examined a paretic spinal fluid which he had kept on ice for over one year. The same typical paretic curve was produced as at the first examination. However, Flesh has observed that in spinal fluids over eight days old the intensity of the colloidal gold curve is greater.

The Wassermann Test. In doing our Wassermann test we use for antigen an alcoholic extract of human heart. In our experience the cholesterinized antigen is so sensitive that we have obtained positive findings in apparently normal cases when other antigens also gave negative findings. Of course, there is the possibility of getting a negative test in weakly positive cases with an antigen similar to the one we use. We inactivate all sera, but use the spinal fluids direct in quantities from 0.02 to 1 c.c. In a few negative cases we have used larger amounts with rather unsatisfactory results.

This paper comprises the study of 203 cases: 43 paresis, 34 tabes, 27 cerebrospinal lues, 4 congenital lues, 11 meningitis, 3 tetanus,

and 81 other non-luetic organic and functional conditions. In the luetic cases the report of the first examination is given before active antisyphilitic treatment was commenced. All the tests have been most intense and constant in general paresis.

GENERAL PARESIS—43 CASES.

Case No.	Wasserman.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
15	+	+	5543200000	+	+	64	
19	+	+	4555420000	+	+	92	
29	+	+	5554400000	+	+	24	
30	+	+	5555544432	+	+	106	
31	+ ·	+	5543200000	+	+	42	
32	+	+	5554420000	+	+	12	
33	+	+	5455400000	+	+	16	
34	+	+	5554321000	+	+	29	
35	+	+	5555430000	+	+	83	
36	+	+	5555555555	+	+	37	Acutely maniacal type.
37	+	+	5554200000	+	+	44	
38	+	+	5555421000	+	+	9	
39	+	+	4554200000	+	+	32	
40	+	+	5555430000	+	+	12	
41	+	+	5554210000	+	+	17	
42	+	+	5532000000	+	+	115	
58	+	+	5544311000	+	+	62	
64	+	+	5555410000	+	+	6	
65	+	+	5544300000	+	+	34	
67	0	+	5554320000	+	+	23	
68	+	+	5554310000	+	+	29	
69	+	+	5544420000	+	+	81	
70	+	+	4554430000	+	+	37	
81	+	+	5555430000	+	+	63	
82	0	0	0122200000	Mild	Mild	14	Typical clinical paresis
112	+	+	5555554200	+	+	4	
122	+	+	5555432000	+	+	28	
126	+	+	4555420000	+	+	16	Frequent epilepsy.
136	+	+	5554320000	+	+	46	
139	+	+	5555543100	+	+	38	
150	+	+	5543300000	+	+	6	
154	+	+	5555420000	+	+	8	
161	0	0	5544410000	+	+	64	Grandiose type.
165	+	+	5554300000	+	+	14	
169	0	+	5544421000	+	+	28	
182	+	+	5543100000	+	+	16	
183	+	+	4555430000	+	+	22	
184	+	+	5555555555	+	+	78	Grandiose type.
191	+	+	5543100000	+	+	6	
196	+	+	5554310000	+	+	18	
198	+	+	5544320000	+	+	20	
201	+	+	5554321000	+	+	68	
202	+	+	4554300000	+	+	74	

The characteristic paretic curve of the colloidal gold reaction was found in 42 cases out of 43 spinal fluids examined. Case 82, a typical clinical case of paresis, gave normal blood and spinal fluid findings, and under antiluetic treatment intraspinally made an apparent clinical recovery up to the present time (ten months ago). He had contracted syphilis twenty-two years previous. It is quite possible that we were dealing with a case of cerebrospinal

lues. Subsequent tests made after vigorous treatment showed no change from the first one. One case (No. 161) gave a typical paretic curve with a negative blood and spinal fluid. This case is one of the grandiose type and is clinically undoubted paresis. Case 36 (acutely maniacal type) and Case 184 (grandiose type) were interesting in that they gave complete decolorization in all dilutions. Four of our cases gave a negative Wassermann in the blood; all showed a marked positive globulin test; all but 5 had a lymphocytosis of over ten cells per cubic millimeter. In a study of 130 cases of paretic spinal fluids, Miller and his co-workers found a typical paretic colloidal gold curve 127 times. Of the three atypical reactions, 1 occurred in a very early case, 1 was probably due to an old and infected spinal fluid, and 1 was made after vigorous intraspinal therapy. Other workers do not place as much diagnostic value on this curve. Swalm and Mann and Solomon and Welles, although they found it present in a large majority of their paretics, question its true specificity.

TABES—34 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
6	0	+	3343210000	+	+	16	
9	+	+	5554210000	+	+	38	No signs of paresis.
10	+	+	3334200000	+	+	8	
4	0	0	3443210000	+	+	3	Typical clinical case.
12	+	+	1233210000	+	+	16	
13	+	+	2334310000	+	+	6	
18	+	+	3443210000	+	+	23	
54	0	0	1232100000	0	0	3	Typical case with positive history.
56	+	+	4432100000	+	+	18	
57	+	+	3244210000	+	+	69	
59	+	+	2342123432	+	+	38	
60	+	+	3444310000	+	+	26	
62	+	+	4432100000	+	+	9	
63	+	+	5554321000	+	+	18	Suspected taboparesis
83	0	0	0122210000	0	0	3	Typical clinical case.
86	+	+	2343200000	+	+	79	
87	+	+	4433210000	+	+	16	
88	+	+	3444321000	+	+	8	
109	+	+	2344431000	+	+	19	
124	+	+	1234300000	+	+	6	
125	+	+	4433210000	+	+	32	
155	+	+	5342100000	+	+	8	
170	+	+	2344310000	+	+	26	Gastric crises only.
173	+	+	4432200000	+	+	18	
179	+	+	3344210000	+	+	36	
181	+	+	3334110000	+	+	28	
185	+	+	3444200000	+	+	6	
186	0	+	4322210000	+	+	18	
187	0	0	3444320000	+	+	9	
188	0	+	2223210000	+	+	3	
193	+	+	3443320000	+	+	12	
195	+	+	4342100000	+	+	36	
200	+	+	3443100000	+	+	94	

In our series of 34 cases of tabes we found a positive globulin test in all cases but 2, a lymphocytosis above ten twenty-two times, a positive Wassermann in the spinal fluids in all cases but 4, and a positive Wassermann in the blood in all but 7. There was a definite color change in the colloidal gold solution in the luetic zone in every case except one. In the majority of instances the color change occurred up to No. 4. This is more marked than occurs in cerebrospinal lues, but not sufficiently characteristic to be of much diagnostic value between it and tabes. Case 83 had been previously treated with salvarsan intravenously, had Argyll-Robertson pupil, loss of knee-jerks, shooting pains, and loss of bladder control. Both the blood and spinal fluid findings were normal. However, under further antispecific treatment intraspinally (Swift and Ellis) his lightning pains stopped and his bladder improved. Case 9 gave a typical paretic curve in the colloidal gold solution, but no clinical evidence of paresis. In Case 63, where we have another typical paretic curve, the patient showed evidence of memory impairment, which makes the probable diagnosis one of taboparesis. In Cases 54 and 187 all findings were negative except colloidal gold precipitation in the syphilitic zone.

CEREBROSPINAL LUES—27 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho- cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
2	0	+	1232100000	+	+	16	
7	+	+	1332100000	+	+	9	
8	0	0	1233220000	+	+	21	Positive history.
20	+	+	1332100000	+	+	6	
28	0	+	2343220000	+	+	38	
66	+	+	5555420000	+	+	116	Apoplexy; no mental symptoms.
72	+	+	1232210000	+	+	8	
73	+	+	0123431000	+	+	16	Postmortem, gumma of brain.
80	0	+	1332210000	+	+	3	
84	+	+	2343210000	+	+	29	Major epilepsy.
85	+	+	4323100000	+	+	16	
112	+	+	1133420000	+	+	38	
119	+	+	2234300000	+	+	6	
120	+	+	1234200000	+	+	19	
121	0	0	1333320000	+	+	8	Positive history; typical case.
134	+	+	0133210000	+	+	4	
135	+	+	1233210000	+	+	16	
145	+	+	0123310000	+	+	5	
149	+	+	1334310000	+	+	22	
158	+	+	0234210000	+	+	12	
160	+	+	0122100000	+	+	8	
168	+	+	4555432000	+	+	42	
189	+	+	0123210000	+	+	16	
190	+	+	1334310000	+	+	4	
194	+	+	3332100000	+	+	96	
199	+	+	2334320000	+	+	18	
207	+	+	4543100000	+	+	68	

In cerebrospinal lues (27 cases) the globulin test was positive in all; there was lymphocytosis in 17 cases; the Wassermann in the spinal fluid was negative twice and in the blood negative 5 times. In all cases the colloidal gold test gave color changes in the syphilitic zone. In 3 instances there was the typical paretic curve without any clinical evidence of paresis.

CONGENITAL LUES—4 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
71	+	+	5555431000	+	+	38	Juvenile paresis.
174	0	0	0100000000	0	0	3	After vigorous treatment.
175	+	+	0122100000	+	+	18	Associated with epilepsy.
92	+	+	1111210000	+	+	not done	Primary optic atrophy.

Our 4 cases of congenital syphilis are too few to be of much value, except that they confirm Miller and Levy's conclusions, namely, that in the spinal fluid of congenital luetics the colloidal gold test shows nothing more definite in the majority of cases than the Wassermann. This is all the more interesting when one remembers there is a more positive Wassermann in congenital than acquired lues. In their conclusions, Miller and Levy state that the colloidal gold test has no advantage over known laboratory procedures in the diagnosis of congenital syphilis. However, Grulee and Moody, and also Johnston, in a recent publication, are not in accord with this.

MENINGITIS—11 CASES.

Case No.	Colloidal gold test.	Globulin.		Cell count.	Remarks.
		Nonne.	Noguchi.		
16	0001233110	+ +	+ +	96	Tubercles found in spinal fluid.
61	0002334100	+ +	+ +	116	Tubercles found in spinal fluid.
131	0133432110	+ +	+ +	286	Tuberculous meningitis postmortem.
152	0002333421	+ +	+ +	94	Tubercles found in spinal fluid.
162	0123322000	+ +	+ +	69	Tubercles found in spinal fluid.
203	0001221000	+ +	+ +	192	Clinical tuberculous meningitis.
105	0000133321	+ +	+ +	1260	Pneumococci found in spinal fluid.
108	0001234441	+ +	+ +	116	Pneumococci found in spinal fluid.
106	0022343111	+ +	+ +	492	Meningococci found in spinal fluid.
107	0013443200	+ +	+ +	612	Meningococci found in spinal fluid.
151	0000122100	+ +	+ +	1242	Meningococci found in spinal fluid.

In our meningitis cases (6 tuberculous, 2 pneumococcic, 3 meningococcic) all but two gave the characteristic "Verschiebung nach oben" in the colloidal gold test, namely, a decolorization in the

higher dilutions, but the zone effected or the intensity of the reaction was not constant. The reaction usually becomes more marked as the disease progresses. All gave a marked globulin test and a cell count ranging from 94 to 1242 per cubic millimeter.

CEREBROSPINAL LUES ASSOCIATED WITH PNEUMOCOCCIC MENINGITIS.[2]

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
221	+	+	1124300000	+	+	12	
223	not taken		1121134421	+	+	Many leuko-cytes	Diplococci pneumoniæ in spinal fluid.

A case of cerebrospinal lues with a subsequent pneumococcic meningitis gave the above findings. The variations in the colloidal gold curve were interesting. The pneumococcic meningitis developed one month after the cerebrospinal lues.

TETANUS—3 CASES.

Case No.	Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
		Nonne.	Noguchi.		
204[3]	0003343200	Trace	Trace	4	
205	0000244310	Trace	Trace	8	
206	3443221000	+ +	+ +	Many	Hemorrhagic fluid.

In 3 cases of tetanus the spinal fluid findings were interesting in that the colloidal gold curve showed "Verschiebung nach oben" similar to meningitis. However, the other findings were negative. The Wassermann examined in Case 204 was also negative.

ACUTE ANTERIOR POLIOMYELITIS—4 CASES.

Case No.	Colloidal gold test.	Globulin.		Lymphocytes.
		Nonne.	Noguchi.	
207	1233210000	0	0	6
208	0000110000	0	0	2
209	0000000000	0	0	0
210	0000000000	0	0	8

[2] Reported in full in Jour. Amer. Med. Assn., July 29, 1916.
[3] Wasserman in spinal fluid negative.

MISCELLANEOUS GROUP—76 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
3	0	0	0000000000	0	0	6	Transverse myelitis.
1	0	0	0000000000	0	0	2	Hysteria major.
5	0	0	0000000000	0	0	0	Involutional melan-cholia.
14	0	0	0000000000	0	0	4	Syphilophobia.
17	0	0	0000123110	0	0	6	Spinal cord tumor.
21	0	0	0000000000	0	0	3	Epilepsy.
22	0	0	0000000000	0	0	0	"
23	0	0	0000000000	0	0	2	"
24	0	0	0000000000	0	0	4	"
25	0	0	0000000000	0	0	0	Friedreich's ataxia.
27	+	0	0000000000	0	0	2	Progressive muscular dystrophy.
43	0	0	0000000000	0	0	3	Manic depressive in-sanity.
44	0	0	0000000000	0	0	9	Manic depressive in-sanity.
45	0	0	0000000000	0	0	6	Manic depressive in-sanity.
46	0	0	0000000000	0	0	0	Manic depressive in-sanity.
47	0	0	0000000000	0	0	2	Manic depressive in-sanity.
48	0	0	0000000000	0	0	0	Manic depressive in-sanity.
49	0	0	0000000000	0	0	0	Manic depressive in-sanity.
50	0	0	0112100000	0	0	0	Manic depressive in-sanity.
51	0	0	0000000000	0	0	1	Manic depressive in-sanity.
52	..[4]	..[4]	0000000000	0	0	0	Manic depressive in-sanity.
53	0	0	0000000000	0	0	0	Manic depressive in-sanity.
56	0	0	0000000000	0	0	2	Familial spastic par-alysis.
74	0	0	0000012220	0	0	6	Involutional melan-cholia.
75	0	0	5543100000	0	0	9	Multiple sclerosis.
110	0	0	0000000000	0	0	4	" "
212	0	0	0000000000	0	0	6	" "
216	0	0	0000000000	0	0	8	" "
76	0	0	0000000000	0	0	0	Mother of No. 71.
77	0	0	0000000000	0	0	2	Wife of No. 60.
78	0	0	0122220000	0	0	9	Sydenham's chorea.
79	0	0	0000000000	0	0	4	Huntington's chorea.
89	0	0	0000000000	0	0	6	Delirium tremens.
90	0	0	0112210000	0	0	8	" "
91	0	0	0111211000	0	0	5	" "
92	0	0	0000000000	0	0	4	" "
93	0	0	0112221000	0	0	2	" "
94	0	0	0000000000	0	0	3	" "
95	..[4]	0	0000000000	0	0	9	" "
96	0	0	0000000000	0	0	7	" "
97	0	0	0222100000	0	0	8	" . "

[4] Not done.

MISCELLANEOUS GROUP—76 CASES.—*Continued.*

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
98	..4	..4	0000000000	0	0	1	Delirium tremens.
99	0	0	0000000000	0	0	3	" "
100	0	0	0000000000	0	0	0	" "
101	0	0	0000000000	0	0	2	" "
102	..4	..4	0000000000	0	0	0	" "
103	0	0	0000000000	0	0	6	" "
104	0	0	0000000000	0	0	0	" "
229	..4	..4	0112111000	+	+	..4	Fluid from cerebellar cyst.
113	0	0	0000000000	0	0	2	Acute alcoholism.
114	0	0	0000000000	0	0	0	" "
115	..4	0	0000000000	0	0	1	" "
116	..4	0	0000000000	0	0	3	" "
117	0	0	0000000000	0	0	0	" "
118	0	0	0000000000	0	0	2	Huntington's chorea.
127	0	0	0001223300	+	+	56	Spinal cord tumor.
128	0	0	0012100000	0	0	4	Dementia precox.
129	0	0	0000000000	0	0	2	Uremic convulsions.
130	0	0	0000000000	0	0	3	Syphilophobia.
132	·0	0	0000000000	0	0	9	Cerebellar tumor.
133	0	0	0000000000	0	0	16	Meningismus.
137	0	0	0000000000	0	0	9	Acute mania.
138	..4	..4	0000000000	0	0	8	" "
141	0	0	0000000000	0	0	8	Uremia.
149	0	0	0000000000	0	0	83	Meningismus.
143	0	0	0112221000	0	0	4	Bell's palsy.
146	0	0	0000000000	0	0	2	Migraine.
148	0	0	0000000000	0	0	0	Trifacial neuralgia.
153	0	0	0122210000	0	0	12	Brain tumor.
157	0	0	0000000000	0	0	3	Myasthenia gravis.
159	0	0	0000000000	0	0	1	Brain tumor.
163	0	0	0000000000	0	0	4	Cerebral palsy of childhood.
166	0	0	0000000000	0	0	4	Bell's palsy.
172	0	0	0023455555	..	..	2	5 ? ?
178	0	0	0000000000	0	0	0	Myasthenia gravis.
219	0	0	0000000000	0	0	2	Wife of tabetic.

Spinal fluids from acute anterior poliomyelitis gave nothing definite. All were obtained during the acute stage of the disease. One case (No. 207) gave a colloidal gold curve in the luetic zone. Johnston found this present in 4 cases during the acute stage. He subsequently examined 2 of these after acute symptoms had subsided and in both the colloidal gold curve was negative. He beleves that this occurrence of an early transitory reaction in the syphilitic zone in the acute stage of anterior poliomyelitis suggests an important aid in the diagnosis of this disease.

In our miscellaneous group (76 cases) all findings were practi-

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4 Not done.

5 Transverse myelitis associated with Pott's disease; spinal fluid showed xanthocromia at three separate lumbar punctures.

cally normal. The Wassermann in the spinal fluid in all cases was negative. One blood gave a positive Wassermann, the cell count was normal except in 2 cases of meningismus, in 1 brain tumor and in 1 spinal cord tumor; the globulin test was negative in all but 1. The colloidal gold test showed nothing definite, except occasionally a slight decolorization in the lower dilutions. In 3 cases of multiple sclerosis all findings were negative, but in 1 case (No. 75) the colloidal gold test showed a typical paretic curve with a negative Wassermann test. Similar findings have been reported. Miller and his co-workers report 3 cases; Flesh observed this curve 6 times out of 8 cases examined. Kaplan found it only once in 18 cases; Oetiker reports 1 case. The presence of a "paretic curve" with the other spinal fluid findings negative might be of help in the diagnosis of suspected multiple sclerosis. Occasionally one sees a report of a "paretic curve" with normal spinal fluid findings in other conditions. Oetiker observed this in a case of puerperal eclampsia; Miller in a brain abscess and in a case of cirrhosis of the liver. Case 172 gave interesting findings. The spinal fluid was slightly hemorrhagic (old hemorrhage) and contained an excessive amount of globulin. The patient had an old Pott's disease of seventeen years' duration, and during the past few months gradually developed a transverse myelitis with a flaccid paralysis. Both spinal cord tumor cases (Nos. 17 and 127) gave a decolorization in the higher dilutions.

SPINAL FLUID FINDINGS AFTER TREATMENT, WHERE ALL TESTS SHOWED IMPROVEMENT.[6]

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
37	0	+	3321000000	0	0	4	Paresis.
9	0	0	1232100000	0	0	2	Tabes.
179	0	0	2231000000	0	0	3	"
193	0	0	0000000000	0	0	1	"
186	0	0	1223200000	0	0	7	"

The effects of antiluetic treatment on these tests have been variable. In the main our syphilitic cases have been treated with salvarsan, intravenously and intraspinally (Swift and Ellis method), combined with mercury. In all cases there has been a gradual reduction of the cell count to normal. In the majority of cases the globulin test has become normal while in some it remained slightly positive. In 21 cases of paresis, treated thoroughly, all but 2 gave a negative blood Wassermann. However, in the spinal fluid it persisted positive in every case. Out of 22 cases of tabes treated, 16, or 73 per cent., gave a negative Wassermann both in the blood

[6] For original findings refer to same case numbers in early part of this paper.

and spinal fluid. In only 5 instances of all antiluetic cases treated did we notice any change in the colloidal gold curve, and in only 1 case did the curve become normal.

SUMMARY. 1. The most constant finding in a pathological spinal fluid is a positive globulin. It is indicative of an inflammatory process, but is of no specific import.

2. Pathological cerebrospinal fluids usually show some lymphocytosis. However, the number may be normal. Fluids from cases of meningitis almost invariably give a high cell count.

3. As an index of pathological change in the cerebrospinal fluid the colloidal gold reaction is more delicate than any other test here employed.

4. Normal spinal fluid usually causes no reduction of the colloidal gold. A slight reduction in any of the dilutions is of no diagnostic import, and may occur in normal spinal fluids.

5. Cases of tabes and cerebrospinal lues gives a typical colloidal gold curve in the luetic zone. Although in tabes the intensity of the curve is usually greater, it is not sufficiently constant to be of diagnostic value between the two conditions.

6. In paresis the colloidal gold test is sufficiently frequent and characteristic to warrant the term "paretic curve," and is of great diagnostic value. However, it has been observed in cases of tabes, cerebrospinal lues, multiple sclerosis, brain abscess, and once in puerperal eclampsia.

7. In meningitis the colloidal gold curve usually occurs in the higher dilutions, and is probably of value in the diagnosis of doubtful cases.

8. In spinal fluids with normal findings, except a paretic colloidal gold curve in doubtful cases, the possibility of a multiple sclerosis must be strongly considered.

9. The colloidal gold test is more delicate than the Wassermann test. Spinal fluids from luetics have given a colloidal gold luetic curve with a negative Wassermann. However, we have never observed a normal colloidal gold curve with a positive Wassermann in the spinal fluid. Exceptions to this are the congenital luetics.

10. Under antiluetic treatment there is usually a reduction in the cell count and globulin of the spinal fluid; frequently the Wassermann becomes negative; rarely is there a change in the colloidal gold test.

11. No spinal fluid test (except the presence of bacteria) is specific. Every test is simply that much coöperative evidence and should be combined with the history of the case and the clinical findings.

I desire to express my appreciation to Dr. Leitch, pathologist at Mounds Park Sanitarium, and Dr. Barron, formerly pathologist at the City and County Hospital, for their kind help and interest in the study of our spinal fluids.

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CONCERNING THE CAUSATION OF EDEMA IN CHRONIC PARENCHYMATOUS NEPHRITIS: METHOD FOR ITS ALLEVIATION.[1]

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One of the most striking clinical manifestations of chronic parenchymatous nephritis is the development of edema or anasarca. Its occurrence is intimately associated with a diminished elimination of salts and water, believed to be due to a reduced power of the kidneys to excrete these substances. Those who have had occasion to observe the condition know well the severe proportions which it may assume, the distress which it causes the patient, and the inadequacy of medicinal treatment or the usual dietetic restrictions.

The present communication forms part of a larger study on nephritis begun a number of years ago. Its purpose is to put on record certain facts concerning the nature of the anasarca occurring in chronic parenchymatous nephritis which are of clinical importance and to suggest a new method of treatment which promises to be useful. The reason for selecting this particular phase of the subject is the conviction (gained in the study) that the edema, or anasarca, is one of the most important phenomena in the disease, and that by its alleviation and prevention great progress is made toward ultimate relief of the renal condition.

[1] Read before the Section on Medicine at the New York Academy of Medicine, October 17, 1916.

Ever since Bright's discovery of renal disease the opinion has prevailed that all the phenomena associated with it are attributable to the pathological changes and the disordered function of the kidneys. It is now conceded that the morbid manifestations of chronic parenchymatous nephritis differ from all other forms of renal disease. Its onset, progress, and duration, its tendency to subcutaneous and serous effusions, and the cardiovascular conditions and urinary findings—all differ from those observed in other varieties of renal disease. It is not the object, at present, to discuss the chemical and pathological features of chronic parenchymatous nephritis as a whole, but it is important to note (and the conclusion seems justifiable from the observations thus far made) that among the cases of parenchymatous nephritis there is a group with a constitutional disorder in which the renal and other manifestations are concomitant or secondary in point of development and importance.

Much discussion has been indulged in concerning the origin of edema in nephritis, and many theories have been propounded concerning the mode of its production.

Thus it was[2] believed that the edema was the result of a "hydremia" from the retention of water caused by the inability of the kidneys to excrete it. Cohnheim[3] supposed that the edema was brought about by an increased permeability of the capillary vessels, induced by the malnutrition or poisoning incidental to the nephritis, which permitted fluid to filter through into the subcutaneous tissues and serous cavities. The hypothesis which has received the soundest clinical confirmation, and still retains many adherents, is that of Widal[4] and his associates, which teaches that the kidneys in this disease have a deficient capacity to eliminate salt (sodium chlorid). The accumulation of salt in the body causes a retention of water, thus giving rise to the anasarca. Fischer's[5] view that the edema is due to an "acidosis" has not received confirmation.

These are the principal views concerning the production of effusions in the body in chronic parenchymatous nephritis. They all attribute the phenomenon in one way or another to the retention of water and salt caused by the inability of the kidneys to eliminate them adequately. The position of the kidney in the animal economy is such that alterations in renal function may result from causes outside the kidney, so that the retention of salt and water, with the consequent formation of edema, may be due to other factors than renal insufficiency. It is evident, of course, that no massive effusion could occur without a corresponding retention of fluid, but the cause need not reside in the kidneys.

[2] v. Noorden: Pathol. d. Stoffw., 1906, i, 1043.
[3] Allg. Path., 1880, ii, 432.
[4] Bull. et mém. Soc. méd. d. hôp. de Paris, 12 Juin, 1902.
[5] Nephritis, 1912.

Whereas it is undeniable that a state of hydremia of varying degree exists in chronic parenchymatous nephritis, just how such a condition can produce edema is not at all clear.   In recent work Baehr and I[6] have found that in nephrectomized animals suffering from experimental diabetes a marked state of hydremia develops (increase of 70 per cent. in blood volume) without causing any edematous deposits.   Concerning the view that increased permeability of the walls of the capillaries plays a part in the production of edema, it might be said that modern research indicates that the capillary vessels are less permeable to salt and water in renal disease than they are normally.   Thus in the work of Chisholm,[7] Boycott and Douglas,[8] and more recently that of Bogert, Underhill and Mendel,[9] we find evidence that "the condition of nephritis produced experimentally 'effects an alteration in the permeability of the walls of the capillaries in such a way as to hinder the passage of fluid from the blood to the tissues.'"   Widal's view that the retention of salt is directly and indirectly responsible for the production of edema would be valid on the basis of the evidence furnished were it not for the fact that numerous other affections of the kidneys also cause a retention of salt without ever leading to the development of edema. Other French observers[10] explain this discrepancy by assuming that the retained salt may exist in two states: one in firm combination with the tissue protoplasm—"chlorure fixé"—and the other, being free, "chlorure libre."   The first phase gives rise to retention of salt without producing edema, "retention chlorure seche," the other phase leads directly to the retention of water, thus causing edema— "retention chlorure hydropigène."   The explanation is ingenious but not convincing.   Just why two such states for chloride retention should exist is not at all clear.   One cannot deny Widal's observations on the effect of salt administration on the edema in chronic parenchymatous nephritis.   That is as it should be.   Neither can we gainsay the observation concerning hydremia and the retention of water.   Least of all can we deny the fact that extreme forms of renal disease can exist, causing retention of different urinary substances without producing edema.   Even total anuria of long duration may terminate and give no evidence of edema.   Passler[11] records a case of anuria of eleven days' standing in which no edema developed.

It is evident, therefore, that more information is needed for the elucidation of this perplexing phenomenon.   Some knowledge is gained by a comprehensive study of the blood sera and the effusions, particularly in the light of the newer physicochemical principles.

[6] Epstein, A. A., and Baehr, G.: Jour. Biol. Chem., 1916, xxiv, 1.
[7] Jour. Path. and Bacteriol., 1914, xix, 265.   [8] Ibid., 221.
[9] Am. Jour. Physiol., 1916, xli, 189.
[10] Marie, R.: Semaine méd., 1903, p. 385.
[11] Deutsch. Arch. f. klin. Med., 1906, lxxxvii, 569.

In 1912–1914[12] I published a series of papers recording the results of chemical studies upon blood sera and puncture fluids. The aim of these studies was to ascertain the various changes which the blood undergoes in different types of disease, particularly in respect to the proteins. Whereas no final deductions were drawn then from the variations encountered, certain points were definitely emphasized. It was observed that the proteins of the serum are subject to extensive variations. Whereas normally the blood serum contains 6 to 8 gms. of protein to the 100 c.c., of which a little more than one-third is globulin; in disease the quantity of protein may be very much reduced but the globulins may show both a relative and absolute increase. In the serum of cases of chronic parenchymatous nephritis the protein content shows the greatest reduction; whereas the increase in globulin content is most pronounced, and it may constitute nearly all of the protein present. (See Table I.)

TABLE I.—AVERAGE COMPOSITION OF BLOOD SERA.   GRAMS PER 100 C.C.

	Total protein.	Globulin.	Albumin.	Globulin per cent.
Normal	7.400	2.738	4.662	37.0
Cardiac conditions	6.408	2.240	4.417	33.9
Chronic interstitial nephritis . . .	6.704	2.396	4.310	35.7
Chronic parenchymatous nephritis .	3.928	3.462	0.466	89.2

TABLE II.—AVERAGE COMPOSITION OF EFFUSION FLUIDS.   SEROUS FLUIDS.

Cardiac conditions	3.352	1.199	1.788	43.0
Hepatic cirrhosis	3.174	1.318	1.856	41.0
Chronic parenchymatous nephritis .	0.285	0.285	0	100.0

SUBCUTANEOUS FLUIDS.

Chronic parenchymatous nephritis .	0.098	0.080	0.018	81.0

For reasons which will be given in a future communication I am of the opinion that some of the changes occurring in the proteins of the serum, more especially the globulin content, are the result of well-defined influences acting upon the blood. In contrasting the findings in the sera of patients with different forms of renal disease the conclusion has been reached that chronic parenchymatous nephritis is genetically different from all other forms and that the change in the protein composition plays a direct part in the production of some of its clinical manifestations, particularly that of edema.[13] From a broad, clinical stand-point the cases of renal disease studied may be grouped into three classes.

[12] Epstein, A. A.: Jour. Exper. Med., 1912, xvi, 719; 1913, xvii, 444; 1914, xx, 334.
[13] Ibid., 1914, xx, 334.

1. The cases of chronic interstitial nephritis show no change from the normal in the character of the protein composition of the serum, nor in the ratio which the individual fractions bear to each other. On the other hand, the incoagulable and non-protein N of the serum show marked fluctuations, some of which correspond to the degree of functional deficiency of the kidneys.

2. In cases of localized disease of the kidneys (surgical conditions) the changes in the blood serum are twofold: One concerns the protein and is traceable to infections; the other concerns the non-protein constituents and varies with the amount of destruction of the kidney substance. When infection is present an increase in the globulins is observed similar to that occurring in infections in other localities; the non-protein N increases apparently in direct proportion to the degree of deficiency of the kidney.

3. In cases of chronic parenchymatous nephritis the amount of protein in the blood is markedly diminished. From the evidence which we possess the cause of the diminution of the amount of protein is ascribable largely if not entirely to the loss of protein in the urine. The amount of protein lost in the urine daily may be insignificant, and if immediately replaced may exert no influence on the content of the blood serum. As a rule, however, the loss is very considerable.

Dieballa and von Kétly[14] record a protein output in the urine of 24 gms. I have had occasion to observe an albuminuria of several months' duration, with a daily output of protein ranging from 18.5 to 26.2 gms. Now if we remember that the total protein in the blood averages only about 210 gms. the daily loss of so much protein eventually causes a tremendous drain upon the blood serum unless the deficit is replaced. Under normal conditions the loss of fluid from the blood (hemorrhage or otherwise) is immediately replaced by the passage of fluid from the tissue spaces back into the blood capillaries. The experiments of Turner, Marshall and Lamson[15] and their associates on plasmapharesis (i. e., removal of plasma from the blood) show that the protein content of the serum gradually diminishes under such conditions.

In the nephritic individual the loss incurred may at first be covered so that no diminution in the blood-serum proteins may be evident; but as the disease progresses and the albuminuria becomes more intense the loss may exceed the amount restored, so that finally impoverishment of the serum in proteins results. As a rule the nutritional condition of the patients and the dietetic restrictions to which they are subjected in the course of treatment favor such a development.

The fact is that in chronic parenchymatous nephritis the quantity

14 Dieballa and v. Kétly: Deutsch. Arch. f. klin. Med., 1898, lxi, 761.
15 Jour. Pharmacol., 1915, vii, 129.

of protein in the serum is diminished.   The decrease appears to be proportional to the intensity and duration of the disease.   The reduction in the proten content of the serum is not due to the hydremia.   The work of Dieballa and von Kétly[16] furnishes proof of that.

Neither is the diminution in the content of the serum protein to be ascribed to a migration of the substance through the capillary walls into the tissue spaces.   Chemical analysis of the edema fluids in the pure forms of chronic parenchymatous nephritis (by that I mean instances of the disease without cardiovascular involvement) shows that they are made up principally of salts and water.[17]   The protein content is trifling.   The conclusion is therefore unavoidable that the decrease in the protein content of the serum in these cases is to be attributed chiefly to the loss of protein in the urine.   But what relation does this bear to the production of edema?

In order to comprehend fully the nature of the processes which are active in the production of edema it is necessary to consider for a moment the manner in which the exchange of fluid between the blood and the tissues is regulated.

As stated before the loss of fluid from the blood is rapidly restored by the passage of fluid from the tissue spaces back into the blood capillaries.   Two theories have been advanced to explain this absorption of fluid: (1) the backward filtration theory of Landerer, and (2) the osmotic theory of Starling.   According to the first theory, when the pressure in the capillaries falls below that in the tissue spaces the fluid is forced back into the capillaries.   When the reverse occurs, fluid passes from the capillaries to the tissue spaces. According to Starling there is normally a balance in the production and absorption of tissue fluid between the filtration pressure in the capillaries and the osmotic pressure of the colloids of the blood and tissue fluid.

Plasma and tissue fluid are practically identical in everything except protein.   Starling[18] showed that the blood proteins exert an osmotic pressure of about 4 mms. of mercury for every 1 per cent. of protein.   Normally the plasma contains more protein than the tissue fluid; so that normally an equilibrium is maintained in the to-and-fro movement of fluid by capillary pressure working from the vessels in the direction of the tissues and the osmotic pressure of of the blood colloids acting in the reverse direction.   Usually the osmotic pressure of the blood is greater than that of the tissue fluid because of the greater amount of colloids, and, as a result of this influence, the direction of flow is from the tissues to the blood capillary system.   The effect of the two operating forces is naturally different.   The one, capillary pressure or backward filtration (which is the active force in restoring blood volume after hemorrhage, etc.), must cause the passage of fluid which is approximately of the same

16 Loc. cit.   17 Epstein, A. A.: Jour. Exper. Med., 1914, xx, 334.
18 Quoted from F. H. Scott, Jour. Physiol., 1916, l, 157.

composition as that contained at the source.   For example if trans-
udation occurs because of increased capillary pressure the migrating
fluid must be like that of the blood serum.   This is verified by the
composition of effusions encountered in conditions of static dis-
turbances, such as cardiac disturbances, cirrhosis of the liver, etc.
(See Table II.)   When the capillary pressure is lessened (as after
hemorrhage) the composition of the fluid which passes from the
tissues into the blood stream must be like that of the tissue fluid.
Scott[19] in the study of this subject has shown that the fluid which
passes from the tissues under these conditions contains from 0.6 to
2.09 per cent. of protein.

On the other hand, the fluid which passes in response to the
osmotic pressure of colloids should be practically a solution of salts.
Analysis of the edema fluid encountered in cases of chronic paren-
chymatous nephritis shows the composition to be one of salts and
water. (See Table II.)   The protein content is insignificant and may
be derived from the fluid of the tissue spaces.

We have in these considerations a set of facts which dovetail and
afford us a starting-point for the comprehension of the mechanism
which leads to the production of edema.   It is recognized on the
one hand that the blood serum normally contains more protein, *i. e.*,
more colloid material than the tissue fluid, and that by virtue of this
predominence it possesses a greater osmotic pressure which is vital
in maintaining a balance in the exchange of fluid between the blood
and the tissues.   The examination of the blood sera in cases of
chronic parenchymatous nephritis reveals the fact that the protein,
i. e., the colloid content, is very much reduced, a loss sometimes
equivalent to 60 or 70 per cent. and more of the total serum protein.
In terms of osmosis this loss of protein represents a pressure equal to
20 to 24 mms. of mercury, a factor sufficient to disturb the equilib-
rium in the exchange of fluid between the blood and the tissues.
More precisely the deficit in serum protein causes a fall in the
osmotic pressure of the blood.   This disturbance does not only favor
the passage of fluid from the blood to the tissues, but also gives to
the tissues the controlling power to absorb and retain fluid.

From the very nature of the force which is concerned in the pro-
cess (namely, that of osmosis) the fluid which passes from the blood
to the tissues must be a solution of salts.   The fluids which we find
in the effusions in chronic parenchymatous nephritis are practically
such solutions.   (See Table II.)   As pointed out before, the protein
content is negligible and may not be derived from the blood.

The hypothesis for the production of edema in chronic paren-
chymatous nephritis which I therefore propose is briefly as follows:
The loss of protein incurred by the blood serum through the con-
tinuous albuminuria causes a decrease in the osmotic pressure of the

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[19] Jour. Physiol., 1916, l, 157.

blood, which fact favors the absorption or imbibition and retention of fluid by the tissues. This conclusion gains support from the experiments performed by Tullio Gayda,[20] who found that the edema which is produced in perfusion experiments when normal saline or Ringer solution is used is prevented by the addition to the perfusing fluid of colloids which are in osmotic equilibrium with the colloids of the lymph and tissues. This may not be the only factor but it is an important one.[21] Other evidence is also available to confirm this view, but space will not permit of elaborating further upon this phase of the subject. Suffice it to say that through a change in the protein composition of the blood plasma a condition is produced which is capable of causing the retention of fluid in the tissues.

Certain other factors which are important in the chemical and physical pathology of the disease must be touched upon, as they enter largely into a consideration of the treatment. Whether it be that a state of malnutrition results from the impoverishment of the blood in proteins or that the diseased condition, commonly termed chronic parenchymatous nephritis, is genetically a disorder of nutrition, we find in the blood definite evidence of tissue starvation. The evidence which I have in mind is the remarkable increase in the lipoid content of the blood. A number of such observations are on record. Thus Chaufford, Rechit and Grigaut[22] have noted an increase in the lipoid content. Recently I had occasion to observe very unusual amounts of lipoid substances in the blood serum of cases of parenchymatous nephritis. (See Table III.) The ac-

TABLE III.—CHOLESTERIN CONTENT OF BLOOD SERA. MILLIGRAMS PER 100 C.C.

Diagnosis.	Cases.	Average.	High.	Low.
Chronic interstitial nephritis . . .	24	174	265	100·
Uremia	5	133	194	87
Arteriosclerosis	7	163	218	100
Cardiac conditions	19	157	294 ·	104
Bichloride poisoning	2	127	130	125
Chronic parenchymatous nephritis .	9	559	1230	333

cumulation of these substances in the blood probably arises partly from the mobilization of fat deposits from the subcutaneous tissues and other sources and to a large extent perhaps from degenerative processes in the tissues. The cause of fat mobilization when a lipemia develops may be partly physical displacement, due to the effusions. Usually, however, the condition in the blood is one of

[20] Arch. Sc. Med., 1916, xxxix, 389.
[21] The increase in the globulin content of the blood serum, and the excessive accumulation of lipoids, constitute additional factors which contribute to the causation of edema in chronic parenchymatous nephritis, and interfere with the elimination of salt and water by the kidneys.
[22] Compt. rend. Soc. de biol., 1911, p. 317.

lipoidemia, thus pointing to a metabolic derangement similar to that observed in starvation in advanced diabetes and in pellagra. The degree of nutritional disturbance and fat mobilization can be appreciated only after the cases begin to improve and the edema subsides. Then the patients manifest very marked wasting.

The increase in the lipoid content of the blood is important not only because it gives evidence of a grave nurtitional disturbance but also because it affects the pathology of the disease in other ways. Kaethe Dewey[23] has recently shown that the mere presence of excessive amounts of cholesterin in the blood is capable of producing definite pathological lesions in the kidneys and perhaps also affecting their function. From the work of Mathilde Koch and Carl Voegtlin[24] and also that of Herlizka[25] and Gayda[26] it appears that abstractions of lipoids from tissue cells cause imbibition of fluid with consequent swelling of the cells.

The problem in the treatment of edema in chronic parenchymatous nephritis is to relieve the condition and prevent its recurrence. The mere removal of effusion fluid by paracentesis and puncture, if feasible, may relieve it partly, but does not, as a rule, prevent a reaccumulation. I need not dwell upon the medicinal means used to promote renal activity. The failure of such procedures to influence the edema is classic. It has been shown repeatedly that the kidneys in this type of disease are capable of eliminating the different urinary substances. Their inability to excrete sufficient salt and water is due to causes outside of them.

On the basis of the views presented concerning the causation of edema the real problem in its treatment is the restoration of normal conditions in the blood and the establishment of a healthy state of nutrition. The blood in these cases, as previously stated, shows a marked decrease in protein and an increase in lipoids. The indications are: (1) to increase the protein content of the blood and thus help it regain its normal osmotic power, and (2) to remove or cause the reabsorption by the tissues of the excessive lipoids. The restoration of the protein content may be accomplished by two methods: (1) Massive infusion or transfusion of healthy blood accompanied by the removal of equal quantities of blood from the patient. The latter procedure is necessary to accommodate the introduction of additional blood so as not to embarrass the circulation. It also serves to remove some of the excessive lipoids. (2) Most important is the proper administration of a high protein and fat-poor diet.

The employment of transfusion is undoubtedly helpful and affords a good start in the treatment, but, of course, is not always feasible

[23] Arch. Int. Med., 1916, xvii, 757.
[24] Bull. Hyg. Lab., 1916, No. 103, p. 129.
[25] Arch. di Fisiol., 1909, vi, 369.
[26] Loc. cit.

for obvious reasons. It must be remembered also that whereas the replacement of the impoverished blood of the patient with healthy blood helps toward the restoration of normal conditions, the effect is necessarily only a temporary one, for the continuation of the albuminuria causes a constant loss of blood protein. Chief reliance must therefore be placed upon adequate dietetic measures. The method consists, therefore, in the administration of large quantities of properly selected proteins with a minimum of carbohydrates and the exclusion of fats. The reason for restricting the carbohydrates is twofold: (1) to promote a maximum assimilation of protein, and (2) to exclude the greater production and retention of water which is incidental in the metabolism of carbohydrates. The fats are excluded because of the marked increase of fatty substances in the blood.

DIET EMPLOYED.

	Daily amount.
Food value	1280 to 2500 calories
Proteins	120 to 240 grams
Fats (unavoidable)	20 to 40 "
Carbohydrates	150 to 300 "

ARTICLES USED.

Lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea and cocoa.

As for the administration of fluids and salts, I might say that the fluid allowed is restricted to the quantity present in the food, plus that which is necessary for the comfort of the individual patient, amounting usually to 1200 to 1500 c.c. The amount of salt allowed is the quantity sufficient to make the food palatable.

The method is necessarily slow and requires persistence, but its effect is indeed very salutary. The protein content of the blood increases and the lipoidemia subsides. Accompanying these changes in the blood there is a progressive increase in the excretion of urine with a gradual disappearance of the edema. The albuminuria also diminishes and the patient's health improves steadily.

The diet listed above is relatively low in calories; other articles of food are added gradually as conditions allow. The fats are restricted so long as the lipoid content in the blood remains elevated.

The number of cases treated thus far is not large, but such of them as we had represented extreme types of the disease. The results obtained have been very encouraging. A detailed report of these cases will be published later.

THE COMPLEMENT–FIXATION TEST IN THE DIAGNOSIS OF TUBERCULOSIS, WITH A STUDY OF 135 CASES.

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THE early diagnosis of tuberculosis, or perhaps, more correctly speaking, the determination of the clinical importance of the foci which most of us are supposed to harbor, is admittedly one of the most difficult as well as most important problems in clinical medicine. So many factors have to be considered, and in certain types of cases all the available data are so indefinite, that sometimes the best we can do is to make a more or less accurate guess.

I cannot agree with those who consider the subcutaneous injection of old tuberculin, hitherto the most reliable biological test, an entirely safe procedure. If the injections are given in doses so small that no deleterious effect can be produced, we may fail in clinically active cases to get a definitely recognizable reaction, and then if repeated doses are increased very slowly, immunization may occur. This is what happens with increasing therapeutic doses. Whenever a reaction does occur there is at least a transient lowering of resistance to the infecting germ. This corresponds to Wright's "negative phase," during which phagocytic power, as shown by the opsonic index (and therefore the immunity mechanism of the body), is more or less weakened. Now, in a large proportion of suspected cases this is probably quite unimportant, because it is succeeded by a strongly positive phase. In a smaller group, however, definite harm may be produced. In a patient with a fairly low resistance, for example, and with a focus which is moderately active, the transient lowering of resistance occurring as a result of the subcutaneous test may cause increased activation of the focus, and such an event might easily turn the scale against the patient. This may not be at all obvious at the time, and, in fact, probably would not be, but might manifest itself by later clinical developments, the relationship of which to the tuberculin test might not be suspected.

I am quite well aware that many eminent clinicians, Osler among them, have declared for the harmlessness of the tuberculin test carefully employed. The biological facts above set forth are, however, indisputable, and the conclusion that positive harm might result seems unavoidable. In fact I believe I have seen such results follow its diagnostic use. Klebs[1] says that when carefully used in proper doses and in "properly selected" cases it is free from harmful effects, but adds that it should never be resorted to until

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[1] Tuberculosis, 1909, p. 339.

all other means have failed.   Certainly these are peculiar limitations with which to surround a perfectly safe diagnostic procedure. Lawrason Brown[2] in discussing the therapeutic use of tuberculin appears to offer a plausible explanation of the way in which the anaphylaxis occurs, and the same explanation would seem to apply to the harmful results which might follow its diagnostic use.   He says: "The immunity mechanism seems so adjusted that whatever primary protein escapes from the focus (tubercular) is immediately disintegrated; that is, the lytic process set up by the complement is so active that anaphylatoxin is never formed and the lysis carries the splitting process on to the formation of simpler bodies.   Now, when a sufficient amount, however small, of tuberculin (primary protein) is injected into the body it changes this favorable balance and the action is not carried on so far, and anaphylatoxin results. To stem these anaphylatoxins is at times difficult and their result is disastrous."

The reaction to the diagnostic dose of tuberculin given subcutaneously is undoubtedly an anaphylactic phenomenon.   The patient may practically always "stem" the results, but whether he emerges from the anaphylactic storm of the tuberculin reaction with benefit or harm is difficult to determine; but if the cases are not *properly selected*, a process which may require expert judgment, the result may be "disastrous."   If a strongly positive opsonic phase follows the negative phase of the reaction, a result which we are aiming at in our therapeutic use of tuberculin, which I heartily approve, then the patient may be actually benefited by the tuberculin test.   This reaction corresponds to a therapeutic overdose which we consider objectionable and always try to avoid. It is only when the anaphylactic shock is too prolonged and the opsonic power of the plasma too greatly lowered that the germs may take advantage of the situation to the detriment of the patient.

Aside from the question of the possible hazards of the tuberculin test, what dependence can be placed upon it?   If positive, can we confidently assume that the patient has clinical tuberculosis? If it is negative, can we exclude it?   The answer to both of these questions is no.   Simon[3] says that from 90 to 100 per cent. of the cases of pulmonary tuberculosis give a positive reaction, while 92 per cent. of suspected cases and 56 per cent. of non-suspected cases give positive reactions.   The percentage of positive reactions among cases of clinical tuberculosis is undoubtedly very large, but at least it may fail with lowered resistance, and in the very large group of cases, perhaps only moderately advanced, but with fever, either slight or severe, it certainly cannot be used.   On the other hand, if 56 per cent. or even 25 per cent. of non-suspected cases give a reaction, though I am inclined to think that this is a rather

[2] Am. Jour. Med. Sc., 1912, cxliii, 527.
[3] Infection, Immunity, etc., p. 333.

high estimate, it certainly cannot be depended upon to prove the existence of clinical tuberculosis. The work of Otis, Bandilier and Roepke[4] seems to show that syphilis, in at least its early stages, may give rise to a positive reaction. This is especially important in view of the number of "cross-fixations" which sometimes occur in these two diseases. Independently of positive reactions in cases of syphilis, it may be fairly assumed that a large proportion of the positive reactions occurring in non-suspected cases, either in healthy individuals or those suffering from other diseases, are due to concealed foci, which may be pathologically active but clinically entirely latent. In brief, we find that the subcutaneous tuberculin test is not positive in all cases of active tuberculosis; is entirely inapplicable in the febrile state; habitually disappears in the cachectic state of late tuberculosis; and is not infrequently positive in cases in which no focus can be discovered and which are never known neither before nor after the test to show clinical manifestations of tuberculosis.

We naturally turn therefore with interest, but with not a little habitual distrust, to the complement-fixation test now on trial in the diagnosis of clinical tuberculosis, which is the main subject of this paper. This test has apparently arrived at the point where it offers much of hope without subjecting the patient to the hazards, however remote, of the subcutaneous tuberculin test. The biological basis upon which the tuberculosis complement-fixation is said to rest is substantially the same as in the case of the Wassermann test. There is, however, this difference: complement-fixation in the Wassermann test depends upon the presence of lipoid bodies, which are not at all specific for syphilis but are found in all the trypanosome diseases, and may even be produced by a meal very rich in fats, although in this latitude and with proper precautions no difficulties arise. In the tuberculosis complement-fixation test, however, the complement is said to be bound by an antibody which is absolutely specific and which is produced by the antigenic effect of the tubercle bacilli toxin. It was shown, for instance, by Citron that complement-binding antibodies were found in the blood of normal individuals after the injection of tuberculin. This is presumably the mechanism of the production of complement-binding antibodies in clinical tuberculosis by a process of auto-inoculation. Whether these antibodies will be found at any particular time or not will depend upon two factors: (1) whether toxic bacillary products are at that moment being, or have rather recently been, thrown into the blood from the tubercular foci, and (2) whether there is on the part of the organism an immunity response to the antigenic influence of these toxic bodies. Citron found that the presence of these complement-binding antibodies following the

injection of tuberculin was transitory, and this is precisely what occurs in clinical cases. I have seen a case show 50 to 75 per cent. inhibition of hemolysis in one test and none in a second test made a week later. This is not at all peculiar to tuberculosis complement-fixation. The same thing has been observed in both the Neisser and Wassermann-fixation tests. It is well known that a single negative Wassermann does not exclude syphilis, although we do not therefore reject the Wassermann test as an aid in diagnosis.

As with the Wassermann so with the tuberculosis complement-fixation test, the results appear to depend somewhat upon the antigen used. A considerable number and variety of antigens have been used during the past six years, which is the period covered by these investigations. The antigens are classified by Miller[5] in a recent communication into four groups as follows:

Group I. Bacillary suspensions (which includes that used by Miller).

Group II. Tuberculins or filtrates (which includes Besredka's and Craig's antigens, and with which Bronfenbrenner's work has been done, as well as my own).

Group III. Bacillary extracts (used by Calmette and Masol, Much, Stimson and others).

Group IV. Tissue antigens (used by Bierbaum, Wolff, Eisner), these being analogous, of course, to alcoholic extract of the luetic liver in the Wassermann test.

Craig[6] using a filtrate antigen, made the test upon 166 cases of pulmonary tuberculosis, together with (for control purposes) 150 syphilitics, 100 patients suffering from other diseases and 100 normal individuals. Only two of the last three groups gave a positive reaction with the test. Of the 166 cases of pulmonary tuberculosis, 142 were positive and 24 negative; 107 of these cases were clinically active, giving 103, or 95 per cent., positive. Of the 59 inactive cases, 39, or 66 per cent. were positive. He found sometimes that the same case would give positive and negative tests on different days.

Bronfenbrenner,[7] using Besredka's antigen, studied 625 unselected hospital cases, with special reference to the association of syphilis and tuberculosis in those cases in which both of these diseases were clinically recognized or the patient gave both complement-fixation tests. Included in this 625 cases there were 174 cases of tuberculosis, 65 of which were active. Of the latter, 61, or 94 per cent. gave positive tuberculosis complement-fixation tests while 4 cases were negative. There were 27 cases of tuberculosis apparently undergoing recovery, of which 15 were positive and 12 negative.

There were 108 cases out of the 625 in which a clinical diagnosis

⁵ Jour. Lab. and Clin. Med., August, 1916, p. 816.
⁶ Am. Jour. Med. Sc., 1915, xl.
⁷ Arch. Int. Med., 1914, xiv, 787.

of syphilis was made; 41, or 38 per cent. of these gave a positive tuberculosis complement-fixation test. This is undoubtedly a very large percentage of tuberculosis among syphilitics, and fairly raised the question as to the specificity of the serum test. By a carefully conducted series of experiments, which appear to me thoroughly convincing, he has proved that the two existing positive tests when associated are due to entirely distinct and separate antibodies. He shows very clearly that the tuberculosis complement-fixation reaction is not lipotropic in character. He removes the lipoid substances from the Besredka antigen by extraction with ether without impairing its complement-binding power. He then exhausts the tubercular antibodies by repeated fixations with Besredka's antigen, leaving the Wassermann reaction unimpaired, and then, of course, in another specimen of serum exhausts the syphilitic antibodies by suitable antigens, leaving the tuberculosis complement-fixation test unimpaired. His conclusion that the tuberculosis complement-fixation test is entirely specific, and that the individual giving positive fixation of complement with both this and the Wassermann test has both tuberculosis and syphilis, seems entirely justifiable. We are dealing with two of the most common and most serious infectious diseases, either one of which usually lasts through a long period of years, naturally predisposing to any other infection, and therefore it is not strange that a large proportion of syphilitics should be tubercular, and perhaps the reverse is almost equally plausible, owing to the widespread distribution of syphilis.

Miller,[8] using an antigen prepared by grinding tubercle bacilli with table salt and then adding water up to isotonicity, obtained 229 (98 per cent.) positive complement-fixation tests out of 232 clinically active cases, all of which had tubercle bacilli in the sputum. In 90 inactive or healed cases he found a negative reaction in 83 (7 were positive, and in 5 of these tubercle bacilli had recently been found in their sputum). In 140 cases in which the diagnosis was doubtful 32 gave a positive tuberculosis complement-fixation test. In 45 cases giving the positive Wassermann reaction, unlike Bronfenbrenner, he found only 2 with positive tuberculosis complement-fixation—in one of these the diagnosis of both syphilis and tuberculosis was subsequently established.

It was my intention to have this test made in my clinical laboratory with both the Wassermann and Neisser complement-fixation tests in practically every case, in order to get as broad a view-point of its clinical application as possible in both a positive and negative way. For various reasons this was not fully realized, but during the past year 135 complement-fixation tests have been made. While the number is not large the cases, for the most part, were

[8] Jour. Lab. and Clin. Med., August, 1916, p. 816.

very carefully studied, and it seemed that their analysis, with a brief review of and comparison with other recent work and my own conclusions based thereon, might be of sufficient interest to warrant its presentation.

Craig's antigen and an antihuman amboceptor derived from the rabbit were used in all the work, and the technic employed was that of Noguchi, simply substituting one antigen for another, or using several antigens with the same serum.[9]

For reasons which appear sufficient, clinical importance was attached to smaller degrees of inhibition than with the Wassermann test. If approximately 25 per cent. of inhibition occurred, or even less with perfect hemolysis in the serum control, it was regarded as significant and followed up by further investigation, because the complement-binding antibodies, unlike those in the Wassermann test, are specific. Of these 135 cases, 36 were regarded as cases of tuberculosis upon clinical grounds. In 22 tubercle bacilli had not been found, while they had been demonstrated in 14. Of the 22 with no bacilli present, 18 (or 77 per cent.) gave a positive complement-fixation test and 4 negative, while of the 14 cases with bacilli, 10 (or 71 per cent.) gave a positive and 4 a negative result.

There were 8 cases regarded as simply suspicious. Of these, 2 gave a positive complement-fixation and 6 a negative.

Nine cases, so far as could be determined, were normal in every respect. Of these 1 was positive and 8 negative. The one case giving a positive fixation, and supposed to be perfectly healthy, developed clinical tuberculosis within two or three months, which is now progressing. One other case in this group was regarded with suspicion, but gave a negative result and remains well.

Seventy-four cases were suffering from other diseases but were without suspicion of tuberculosis. Of these, 15 gave a positive and 59 a negative complement-fixation test.

The subcutaneous tuberculin test was made 16 times in the 135 cases. It was positive 4 times and negative 12 times. The 4 cases giving a positive tuberculin reaction all gave positive complement-fixation tests. Of the 12 cases in which the subcutaneous test was negative, 9 gave a negative complement-fixation test and 2 positive; one was positive at one time and negative at another.

In regard to the very interesting question of "cross-fixation" with the Wassermann test, my results are perhaps somewhat more discouraging than Bronfenbrenner's. In 95 cases both tests were made. There were 25 positive Wassermanns in the total of 95. Of these, 11 (or 44 per cent.) gave a positive tuberculosis complement-fixation test. This is 6 per cent. higher than that obtained in Bronfenbrenner's cases. In this connection it might be remarked that of the 11 cases with positive Wassermanns which also gave

positive tuberculosis complement-fixation tests in 2 the clinical evidence was in favor of tuberculosis and in 9 against it. In two or three tuberculosis was plausible and in the remainder very improbable. Of the 70 with negative Wassermann, 20 gave positive tuberculosis tests or 28 per cent. as against 44 per cent. of those with a positive Wassermann. Of the cases with a positive tuberculosis complement-fixation test in which also the Wassermann was made, 31 in number, 11 (or 35 per cent.) had positive Wassermanns.

The results obtained by Miller with the bacillary suspension and by Bronfenbrenner with the tuberculin type differ remarkably in the "cross-fixation" obtained in cases with a positive Wassermann. In 45 cases of Miller's giving a positive Wassermann, 2 gave a positive tuberculosis complement-fixation, while Bronfenbrenner found in 108 cases of syphilis in which tuberculosis was not suspected, 41 cases (or 38 per cent.) giving positive tuberculosis complement-fixation. On the other hand, Craig, using an antigen of the same type as Bronfenbrenner, with some difference in the technic of preparation did not get a single positive tuberculosis complement-fixation in 150 cases showing a positive Wassermann. These discrepancies are somewhat difficult to reconcile. In both Craig's and Miller's cases of syphilis the percentage of cases giving positive tuberculosis complement-fixation is smaller than the actual number of cases one would expect to find in such a group, while in Bronfenbrenner's and in my own it is undoubtedly very large.

What then is the real clinical value of the tuberculosis complement-fixation test? As indicated at the outset the real problem is not to determine the presence or absence of tubercular foci in any part of the organism but the clinical importance of such foci. We content ourselves by classifying the cases as active and inactive. Let us inquire just what we mean by these terms. Obviously the question of activity may be considered from either a pathological or clinical view-point, the latter always including the former. The case is clinically active only when it is manifested by symptoms or signs, or both. In the absence of clinical manifestations a tubercular focus may be mildly active without disturbing its host, or even entirely quiescent, but the tubercle bacilli are still viable and capable of renewed activity under favorable conditions. Between the foci which are pathologically completely quiescent and those which are producing more or less severe clinical manifestations there must be a group of "border-line" cases which might readily pass into one or the other of these classes, i. e., active or inactive, and which clinical observation and the autopsy room prove to us do actually migrate back and forth perhaps many times. The criteria heretofore available for gauging the clinical status of the "border-line" case have been unsatisfactory. The presence even of tubercle bacilli in the sputum only proves that a focus which indeed may be very small and producing no constitutional

disturbance, and would be entirely unrecognizable but for these bacilli, is discharging its contents into a bronchial tube. Such a focus might or might not pour toxins into the circulation, and upon whether it does so or not would naturally depend the presence or absence in the blood of complement-binding or other tubercular antibodies. The absence of tubercle bacilli from the sputum is equally inconclusive. The same thing may be said of the subcutaneous tuberculin test. Physical signs also fail us because they are not always recognizable when most needed and they may be obtained in a healed or rapidly healing focus. In view of all these facts and the demonstrable inconstancy of tuberculosis complement-binding antibodies, what can be reasonably expected from the complement-fixation test? While I believe that this test has arrived at the stage of clinical usefulness, yet its limitations are clearly defined. The absurdity of basing a clinical diagnosis upon any single laboratory test must be obvious to anyone upon the slightest reflection. This may be unfortunate, but in spite of these limitations the clinician should accept the information which it gives at its face value and make it a part, but only a part, of the basis of his clinical judgment. Viewed in this, its proper light, my own conviction is that with either the Besredka, Craig, or Miller antigen it is probably as reliable as and much more widely applicable than the subcutaneous test without the hazards of the latter. The positive complement-fixation obtained in unselected cases with varying pathology probably represents the "border-line" cases above referred to. Bronfenbrenner found 8 per cent. of 75 such cases giving positive fixation. In my own series of 65 such cases, 13 (or 20 per cent.) gave a positive complement-fixation test. My own results in this class of cases were in remarkable contrast to those of Craig, using presumably the same antigen. My own antigen was not made by Craig, however, but in one of our large biological laboratories,[10] and it may have varied slightly from Craig's formula; and then, too, it is possible that in the class of patients with which Craig had to deal, presumably men accepted for service in the United States Army because of their freedom from disease, tuberculosis may have been exceptionally rare, and, of course, by the very terms of his classification a case of suspected tuberculosis would be eliminated from this group. In spite of all this, however, it is remarkable that in 100 patients suffering from other diseases, everyone of them should have given a negative complement-fixation test. In view of all the facts, and in spite of some discrepancies, I believe, with both Bronfenbrenner and Craig, that the tuberculosis antigen will not fix the complement in the presence of syphilitic lipoid antibodies unless tubercular antibodies are also actually present. The vital question as to whether the tuberculosis complement-

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[10] Parke, Davis & Co.

fixation test can distinguish between clinically active and inactive cases cannot be given a positive answer excepting with the qualifications above indicated. Bronfenbrenner cautiously says that it seems to answer the requirements both of early diagnosis and of differentiation of active tuberculosis from that in which the pathological condition has apparently been arrested. This is safely conservative, but does not cover the "border-line" cases already referred to. Miller says that with his antigen inactive cases, as a rule, are negative. It seems to me that our conclusion at present must be that complement-binding antibodies are or may be present in the blood of both clinically active and inactive cases; that they may be intermittently absent in both groups of cases but more constantly present in active than in inactive cases, and that the fact of their presence as revealed by this test is valuable information which decides nothing but the existence of a focus which is at least pathologically active.

SUMMARY. Specific complement-binding bodies are present in the blood of patients suffering from tuberculosis. They are not constantly present even in clinically active cases and may be present in cases which have no clinical manifestations. Their presence may be reliably demonstrated by the usual technic. A positive result proves the existence of a tubercular focus, which is at least pathologically active. Its clinical importance, and its relationship to any coexisting syndrome, can only be decided by correlating it with all available clinical data, precisely as in the case of a positive Wassermann in an obscure case. A negative fixation test does not absolutely exclude clinically active tuberculosis any more than a single negative Wassermann excludes clinically active syphilis.

With antigens made from tuberculins or bacillary suspensions the results are at present probably as dependable as the subcutaneous tuberculin test. It is equally applicable in all cases at all times, regardless of fever, low resistance, etc. The subcutaneous tuberculin test, aside from being absolutely prohibited by universal consent in a large group of cases, has in it an element of possible danger difficult to estimate because of the possible or even probable remoteness of effect. Cross-fixations with the Wassermann test mean both tubercular and syphilitic foci. The tuberculosis complement-fixing antibodies are not lipotropic in character but are specific.

While some striking discrepancies exist in clinical reports, the main facts are unimpaired and with due regard to its obvious limitations, the tuberculosis complement-fixation test is a valuable addition to our diagnostic methods.

I wish to express my indebtedness to my clinical assistants, Dr. M. F. Porter, Jr., Dr. B. M. Edlavitch, and Dr. G. B. Kramer for their coöperation in this work.

REPORT OF A CASE OF SCLERODERMA OF THE SKIN.

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The average occurrence of the idiopathic, atrophic dermatitides taken from five large skin clinics in this country and abroad is 1 in every 2580 cases. Since it is so rare, but few cases come under the observation of any one man. To know the different manifestations, symptoms, and complications it is necessary to rely on the experience of others. The greater the number of cases considered the truer the deductions will be drawn. So each case reported will add to the general knowledge of this idiopathic condition.

While reviewing the available literature on this subject the cases reported were tabulated in regard to age, sex, parts affected, and sequence of onset, duration, occupation, treatment, results, and complications. Special note was taken to the frequency of other associated diseases, especially syphilis, tuberculosis, diseases of the thyroid, Raynaud's disease, Addison's disease, and others.

Since this condition was first described by Thirial,[1] in 1845, under the name of ichthyosis, and later in 1854 by Addison,[1] "On the Keloid of Alibert," there have been numerous classifications and names applied to the various forms, all being based on the cutaneous manifestations. There are probably four types which are most generally recognized. Morphea is the name applied by Erasmus Wilson when the condition is that of a circumscribed scleroderma. Scleroderma is a name introduced by Kretschmann. It is defined by Osler as "a nutritional disturbance of the skin, patchy or diffuse, leading to induration and atrophy; usually considered to be a trophoneurosis, the characteristic lesions being areas of skin which are waxy and edematous-looking, surrounded by a violaceous areola, and which gradually become brown, tense, hard, and hide-bound, with increase in collagenous material."

If with this condition contractures are present it is called sclerodactylia.

In 1902 Herxheimer and Hartman classified a group of cases, having similar appearances, under the heading of acrodermatitis chronica atrophicans, the characteristics of cases in this class being:

1. Onset is usually on the backs of the hands and feet, slowly advancing toward the knees and elbows.

2. The disease consists of inflammatory and infiltrative formations, which culminate in atrophy. The atrophy is of a peculiar, wrinkled, cigarette-paper type, to which Jadassohn applied the term "anetodermie."

3. In the edematous stage scleroderma does not show inflammation; this type does.

4. The skin is not hard and adherent, as it is in scleroderma, but is soft and velvety.

5. The presence of an ulnar band, or analogous band of affected skin on legs, and of an immune area, described by Wise, around the genitalia and Scarpa's triangle.

Since 1902 many cases have been reported as belonging to this class. There has been much controversy as to whether these types were different stages in the same process, whether they were different manifestations having the same etiology, or whether they were separate conditions and had different causes. Herxheimer and Hartman, Wise and Snyder and others believe that in acrodermatitis chronica atrophicans the symptom-complex is peculiar to itself and that the constant clinical characteristics, especially the transition from infiltration to atrophy, fully justify its separation from the other forms of diffuse, progressive, cutaneous atrophies.

In tabulating the cases reported an attempt was made to classify the cases under the four divisions above mentioned. This was soon found to be impossible for three reasons: (1) many of the cases presented characteristics of two or more classes; (2) some progressed from one type into that of another; (3) most of the cases were described with such brevity that no classification could be attempted.

The same difficulty was experienced in attempting to classify the case here reported. When first seen the predominating characteristics were those of a disseminated, symmetrical scleroderma. There were areas of waxy or ivory-like spots, surrounded by a violaceous areola. There were areas of atrophic skin that were stiff and adherent, and which could not be picked up between the fingers. The immune area of Scarpa's triangle, described by Wise and Snyder as one of the characteristics of acrodermatitis chronica atrophicans, showed the most marked involvement. The skin over the left ulnar region was of the waxy-edematous type. Over the knees there were patches of the waxy type surrounded by firm, violaceous skin. While under observation the skin in her left forearm changed from the white, edematous type to the pink, atrophic stage, showing the typical ulnar band. The other white areas decreased in size. The hard, adherent, atrophic skin over the hips and sides became softer, more wrinkled, and could be rolled between the fingers—the typical anetodermie of Jadassohn. Histological examination showed less cellular infiltration and more atrophy, so at present this case would be classified probably as a typical case of acrodermatitis chronica atrophicans.

CASE REPORT. The patient is a German woman, age fifty-seven years. She entered Lakeside Hospital June 1, 1915, complaining

of stiffness of the skin, associated with a pricking pain in the affected areas:

Family History. Her father died as result of an accident. Her mother died from apoplexy, at the age of seventy-four years. She had three brothers, two died in infancy and the other one from typhoid fever. One sister is living, but probably has tuberculosis. There is no family history of cardiac or renal disease, rheumatism, insanity, or syphilis.

Personal History. She had chicken-pox and measles when a child. During the past twenty years she has had occasional attacks of articular rheumatism.

Head. She has had severe, throbbing, occipital headaches for a number of years. They are worse at night. In the last four years she has had frequent dizzy spells, often followed by fainting.

Eyes. In June, 1914, while sitting sewing she had a peculiar sensation in her head, and then became unconscious. She regained consciousness the next day. Following this she felt very weak and there was a ptosis of her right eye, which gradually cleared up. Since then she has had some diplopia with increased lachrymation. The throbbing headaches have been more frequent and she often experiences a sound which she describes as of escaping steam.

Ears. Four years ago she had a bilateral suppurative otitis media. This was more severe on her right side.

Nose. Until the age of eighteen years she had very frequent and severe attacks of tonsillitis. Her gums bleed easily. She wears an upper plate; there are frequent sores on the mucous membranes.

Neck. At the age of eleven years a very large abscess developed on the left submaxillary region. In about five weeks this opened spontaneously with a very profuse discharge. The sinus was slow in healing.

Cardiorespiratory. When ten years old she became frightened and ran a great distance. The next day her hands and feet became swollen. She was confined to bed for several weeks. Since then she has palpitation and dyspnea on exertion. She is subject to colds and has a chronic morning cough. She has frequent attacks of pleurisy and occasionally night-sweats.

Gastro-intestinal. About eighteen years ago she had two attacks of peritonitis and four years ago was jaundiced. Her appetite has been good but her digestion has been poor, having flatulence after meals, especially if she eats meat. She vomits frequently and is constipated. She has had two operations for hemorrhoids. With the one a year ago a mass was removed from her rectum, and there was a partial stenosis resulting from the first operation.

Genito-urinary. She has had pyuria, dysuria, incontinence, and frequency of urination for years. She denies ever having had a venereal disease, but thinks her husband did.

Menstrual. Menses began at the age of sixteen years, was always irregular, small in amount and painful, and of about three days' duration.

Marital. Married at the age of seventeen years. She has had nine pregnancies, all the labors being difficult. There were two miscarriages. One child died of diphtheria and measles and one of

FIG. 1.—Showing involvement of the skin of arms, abdomen and legs. The "immune area" below Poupart's ligament is affected the most. The scar shows where a section was removed.

pneumonia. She now has five children, living and in good health. Her husband is dying from carcinoma of the liver.

Habits. Previous to four years ago she always slept well, worked hard, and had a good appetitite. She drinks one cup of tea or coffee with her meals, and does not use alcohol or drugs. Average weight is 220 pounds.

Nine years ago (1906) she observed a small pin-point elevated

red spot on the skin under her right breast the size of a large bean. It was removed by application of caustics. During its removal her right arm became paralyzed and remained that way for two months.

Present Illness. The patient dates her present illness back five years (1910). At that time she had an abscess in her right hip. This was incised and drained. Immediately following this opera-

Fig. 2.—Showing anetodermia of thigh and location of section removed.

tion her hands and feet became swollen. The right middle, ring, and little fingers were affected first. When the left fingers and hand became swollen. On the dorsum of the second phalanx of the right middle finger there would appear a transitory purple color, and coincident with it a tingling sensation. This discoloration and tingling sensation soon involved the fingers of both hands. She could not bend her fingers, due, she thinks, to the swelling. The

skin affected would not perspire, but her head perspired very freely. Three years ago she took some electric baths. This caused the skin to perspire. The swelling and stiffness diminished. While taking these baths a small white elevated nodule, surrounded by a violaceous color, was observed in the left Scarpa triangle. The discoloration gradually enlarged until it involved both hips and legs above the knees.

February 1, 1913, her rectum was operated on. Following this operation her hands again became swollen and painful. The discoloration present only on the legs and hands was now observed to spread over her abdomen as far as her breasts.

Fig. 3.—Section removed from area shown in Fig. 1, showing marked cellular infiltration of the corium, and a diminished papillary layer.

On the back of her right wrist there appeared at this time a mass about the size of a walnut. It was soft and movable, and the skin was movable over it. She observed crepitation when she moved it. She massaged this mass and in nine months it had disappeared, together with much of the swelling.

June, 1915, a similar mass appeared on the back of the left wrist and still is present.

During the last three years locomotion has been interfered with, due to the stiffness and fixation of the skin over the joints. She has found that cold aggravates the condition and increases the discomfort; also the presence of meat and fish in her diet. For the past eight months she says the skin of her face feels stiff, as though there were a tight band around her forehead.

There have been no areas of gangrene or ulceration. Over the hips, where the skin is very tense, there has been an occasional fissure, which has always healed rapidly.

Physical Examination. The patient is a well-developed, well-nourished German woman, of average intelligence. She lies in bed, active dorsal position, complaining of a burning discoloration of portions of her body.

Head. Is well formed. There is no tenderness or deformities.

Ears. The left aural canal is filled with cerumen. Bone conduction is better than air conduction on that side. The right membrane is thickened. Hearing is diminished on this side and air conduction is better than bone conduction.
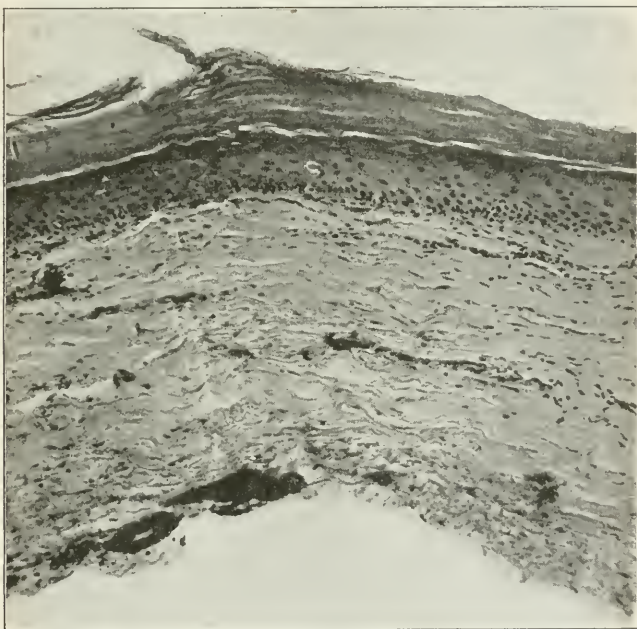
FIG. 4.—Section from area shown in Fig. 2, showing no cellular infiltration, complete absence of papillary pegs, and atrophy of epithelium.

Eyes. There is no ptosis, strabismus, nystagmus, or exophthalmos; the pupils are equal and regular. They react to light and accommodation; extra-ocular movements are good.

. *Neck.* There is a higher pitched note to percussion at both apices, with a few fine, moist rales audible at the right apex. There is a soft, blowing murmur accompanying the diastolic sound and heard best over the aortic area.

Blood-pressure. Systolic, 132. Diastolic, 70. Otherwise the examination of thorax, heart, and abdomen is negative.

Extremities. Flexion and extension is limited in the left knee, due to the stiffness of skin. There are some varicosities. Glands are not abnormally enlarged.

Reflexes. The knee-kick, biceps, triceps, supinator longus and abdominal reflexes are active and equal. The Achilles could not be elicited.

Neuromuscular. There is no acro-ataxia. The proximal ataxia is doubtful. She has a positive Rhomberg's. No Babinski, Gordon, or Oppenheim. Sensation of touch and vibration is perceived
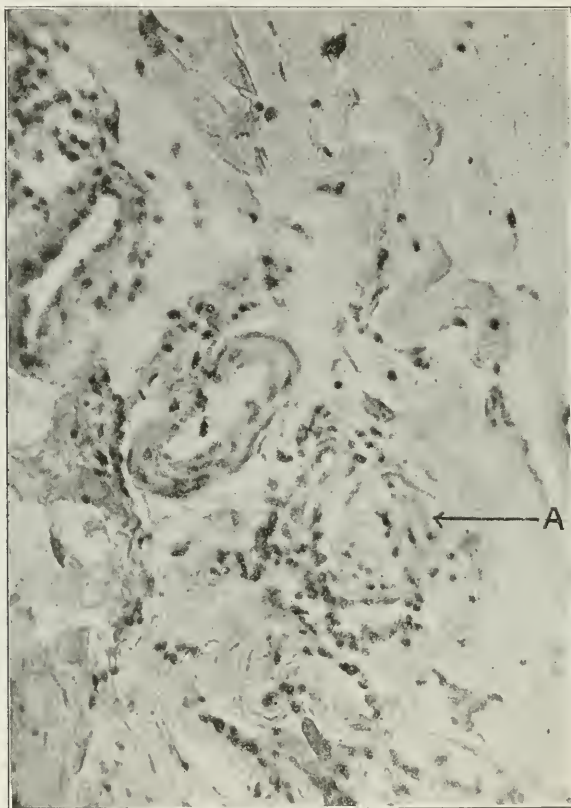
Fig. 5.—Section through a vein, artery, and nerve, which shows cellular infiltration and edema of the nerve (*A*).

throughout. Pain is perceived, but there is an apparent delay of three seconds in transmission. Temperature is less acutely perceived over the affected areas.

Cranial Nerves. There is no disturbance of the cranial nerves with the possible exception of the seventh. The labionasal sulcus is deeper on the left isde; the left angle of the mouth is raised

higher when she smiles. There is the subjective sign of diplopia, but no objective signs of any disturbance in the extra-ocular movements.

Skin. There are three stages represented on the skin. (1) Areas of white, opaque, or waxy, swollen appearance. There are two such areas, about the size of a dollar, one on each side of the umbilicus, and one about twice that size over each gluteal muscle. One above the left patella and on the ulnar aspect of the left arm. (2) Surrounding these areas the skin is smooth, edematous-looking,
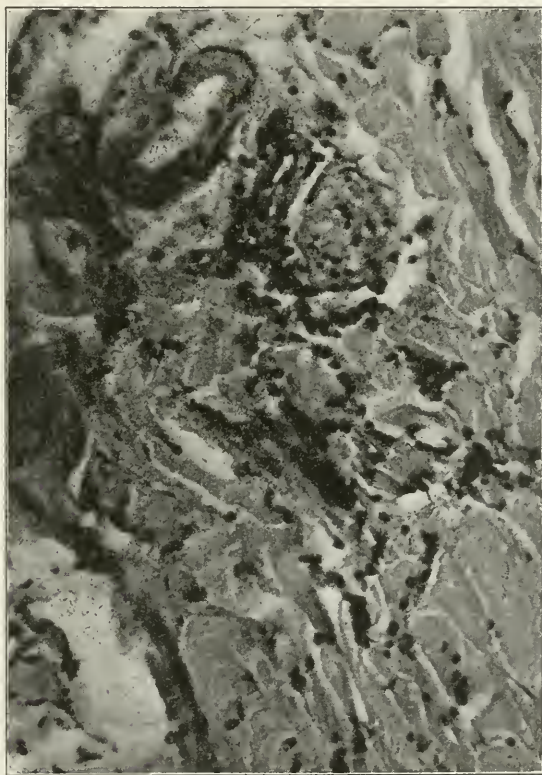
Fig. 6

and of a translucent, violaceous tinge. In places the veins are very easily seen through this. From the breasts down to a point midway between the knee and thigh there is a gradual transition from the smooth, violaceous appearance to the third stage. (3) Here the skin is brown, wrinkled, resembling crumpled cigarette paper, quite thin, and over the hips adherent. In places it is scaly. There are patches of this type of skin on the dorsum of her left ankle, both sides of her knees, both axillæ, and extensor surfaces of both elbows.

Over the joints the skin is not as wrinkled, but it is hard and tense, and cannot be picked up between the fingers.

There is a small, pea-sized nodule in the left Scarpa triangle. It is brown and slightly elevated, and is in the integument.

Laboratory Examination. Hemoglobin, 80 per cent.; red blood count, 4,840,000; white blood count, 6600; differential count of 300 cells: large mononuclear, 8 per cent.; small mononuclear, 18 per cent.; transitionals, 4 per cent.; polymorphonuclears, 68 per cent.; eosinophiles, 2.2 per cent.; basophiles, none. No abnormal red blood cells were seen.

Spinal fluid was clear, but under increased pressure. Pipette count 5 per c.mm. Sicard: 3 cells per high, dry field (all mononuclear lymphocytes). Noguchi's and Fehling's tests were negative. Wassermann reaction negative on blood and spinal fluid. Urine analysis negative.

Subsequent Course. Patient has a constant elevation of temperature of 100°. She could not remain in the hospital on account of sickness of her husband, but promised to return when unencumbered by him. Thyroid treatment discontinued after four days, and she received no therapy until the second admission, Octover 19, 1915, her husband in the meantime having died.

October 19, 1915: Patient again entered the hospital for further observation. At this time she complained of throbbing pains over the abdomen, left leg, and arm. There has been no change in the physical findings, except in the skin.

At this time the skin of the face is not visibly affected. Over the thorax the condition is the same, except that the discoloration has extended on the right up over the clavicle. The two waxy areas below the umbilicus are smaller. On the back, in the rhomboid space, there is a faint violaceous discoloration that was not present before. The waxy area on the left ulnar area has now become of a pinkish hue, and is less edematous in appearance, more translucent, and the veins easily seen.

The violet patches around the knees and ankles are larger. The skin over the abdomen and hips is softer, more pliable, and less scaly. The lump on the dorsum of the left hand is unchanged.

Sensations of touch, pain, and temperature are present and equal throughout; sensation of vibration is diminished over the affected areas.

Blood Examination. Hemoglobin, 80 per cent.; red blood count, 4,440,000; white blood count, 6400; differential count of 200 cells: Large mononuclears, 5.5 per cent.; small mononuclears, 16 per cent.; transitionals, 4.5 per cent.; polymorphonuclears, 74 per cent.; eosinophiles, 2.5 per cent.; basophiles, 1.5 per cent.

Gastric and Duodenal Examination. A duodenal tube was passed on a fifteen-hour fasting stomach. Gastric secretions were clear and opalescent, with a small amount of mucus: Free HCl, 0. Total

acidity, 20. No blood or bile. Duodenal secretion obtained in thirty minutes, a clear amber. No mucus; no blood; free HCl, 0. Total acidity, 14. Lactic, 0. Microscopic examination showed no pus, abnormal detritus, or cellular elements.

Patient was now having an evening elevation of temperature to 101°, with no physical findings to account for it.

She was put on a constant diet of protein, 75 gms.; carbohydrates, 200 gms.; fats q. s. to make 1600 calories. Her total nitrogen, blood-sugar, and sugar tolerance while on this diet was estimated. She was then given thyroid extract, gr. 5, t. i. d., p. c., and again estimated her blood-sugar, sugar tolerance, and total nitrogen. The results are charted below. The sugar-tolerance test was not satisfactory, for the patient vomited a small amount of glucose; the second time there was such a small amount of sugar in the urine that a quantitative test could not be made. However, by using Folin's method of extracting the creatinin and centrifuging the reduced copper was obtained and the amount estimated by Bertrand's method. The amount was too small to be read on Bertrand's table in terms of sugar, so the results only show the amount of copper reduced and not the amount of sugar.

Patient was discharged November 10, 1915, with instructions to continue the thyroid and dilute hydrochloric acid. She was seen at intervals in the dispensary by Dr. Cole. She developed marked palpitation and was very nervous, so the thyroid was discontinued.

January, 1916, she began to have a sanguineous discharge from her vagina, and again entered the hospital on the gynecological service. A dilatation and curettage was done and the curettings were found to be normal. While under the anesthetic two more sections of skin were removed.

On her last admission, January 20, 1916, the skin was much softer. The violaceous band extending over her right clavicle had disappeared. The areas around the knees and ankles were smaller and softer. The lump on the dorsum of her left hand had entirely disappeared. Subjectively she was more comfortable. There was no tingling sensation in the skin, and she complained less of stiffness. There is now a definite violaceous ulnar band on her left arm. The points of interest in this case are:

The mode of onset on the distal parts, following infection and operations.

The formation of subcutaneous nodules, described in other cases reported by Stebbing, Kingsbury and Bromwell.

The presence of an ulnar band, which Herxheimer, Hartman and Wise lay stress on in the so-called cases of acrodermatitis chronica atrophicans.

The most marked involvement of Scarpa's triangle, which is described by Herxheimer, Hartman and Wise as usually unaffected.

The improvement observed with thyroid extract and with care in improving the gastro-intestinal function.

DAYS	1	2	3	4	THYROID EXTRACT GRS. V.T.I.D.P.C.				
					5	6	7	8	9
TOTAL 14 GM NITROGEN EXCRETION 13 GM IN 24 HRS. 12 GM				NORMAL EXCRETION FOR DIET GIVEN					
11 GM									
10 GM									
9 GM									
AMOUNT OF URINE IN 24 HOURS	1700 C.C.	2000 C.C.	1400 C.C.	1000 C.C.	1000 C.C.	1800 C.C.	LOST C.C.	1845 C.C.	1935 C.C.

Pathological Examination. Two sections of skin were removed in June, 1915, a local anesthetic of novocain being used. The tissue was fixed in 4 per cent. formalin. One section was taken from the edge of the white waxy area on the right side of her abdomen. This section also included a piece of the surrounding violaceous area. Another section was removed from her left buttock, where the skin was thin, hard, wrinkled, adherent, and of a brownish hue.

In January, 1916, while the patient was under a nitrous oxide anesthetic, a piece was removed from her side where the skin was extremely thin, non-adherent, and having the typical appearance of wrinkled brown cigarette-paper. Specimens were fixed in alcohol, Zenker's, and 4 per cent. formalin. Stains were made with hematoxylin and eosin, Weigert's, Van Geison's, Unna's orcein, methylene blue, and eosin.

From the examination of the different sections obtained it was apparent that each section showed one stage of a general process, and that this process was of two general types, beginning with inflammation and terminating in atrophy. The earliest changes noted were found in sections of the waxy area on the abdomen: These sections showed no parakeratosis. The stratum lucidum was fairly well defined. The stratum granulosum was present, but not well defined. The stratum spinulosum was reduced in thickness and intercellular bridges were short. The basal cells took a weak stain and showed some vacuolization. Papillæ were present but were small.

Pars Reticularis. In the upper portion of the pars reticularis, immediately beneath the pars papillaris, the collagenous material

stained weakly and was more homogeneous than lower down. It showed fine fibrillary structure. There were occasional groups of small lymphocytes with a few plasma cells. The bloodvessels showed no changes in number, size, or thickness, but there was a slight cellular infiltration around them. Elastic fibers were present.

The middle and lower portions of the pars reticularis showed bundles of collagenous material, staining well, and in places separated by groups of lymphocytes. The lymph spaces were large. Elastic tissue was present. The bloodvessels here showed some endothelial proliferation. There was a marked infiltration around the bloodvessels and sweat glands. Subcutaneous fat was present.

The nerves showed a slight thickening of the sheath, with a cellular infiltration, not only around the nerves but also in them, mostly lymphocytic in character. There was a marked parenchymatous degeneration, and but few axis-cylinders were visible.

The sections obtained from the skin of the buttock showed a greater inflammatory condition, with more atrophy, than the sections from the waxy area. The cells in the stratum granulosum were flatter. The stratum spinulosum was thinner; papillæ were nearly absent.

In the pars reticularis the collagenous material was more widely separated. The cellular infiltration was very marked. The bloodvessels were thicker and showed more proliferation than in the first stage. Fibroblasts were more numerous in these sections. There was the same infiltration of the nerves.

In the sections removed from the side the skin was very thin and wrinkled, showing the most atrophy. Here the stratum lucidum was not so well defined. The stratum spinulosum was very thin, the intercellular bridges were short, and there was a complete absence of papillæ.

The collagenous bundles in the pars reticularis were thinner and separated more. There was less cellular infiltration in the skin from this area than was found in the other sections. Elastic fibrils were present, but they were thin and few in number. There were few sweat glands, which, however, were atrophic. There was no subcutaneous fat.

The histological findings in the cases reported have been practically the same as was found in this case, with the exception of the involvement of peripheral nerves and the presence of elastic fibers. In most of the cases there has been a diminution of the elastic fibers in the inflammatory stages and a complete absence in the atrophic stage. In this case they were present in all stages, but somewhat diminished in the atrophic stage.

There was only one other case found in the literature reviewed that showed involvement of the peripheral nerves. Lindsey Steven found in a case that the nerve fibers from the cervical and lumbar plexus showed a well-marked parenchymatous degeneration.

Herxheimer and Hartman, Kansky and Sutton, MacKee, Howell
and Wise found no changes in the peripheral nerves. Osler in one
case found a thickening of the sheath. However, the change was
so marked in our case that we believe great stress should be laid
on it.

CLINICAL CONSIDERATIONS. In the cases reviewed the ages
varied from nine years to seventy years, the average being thirty-
eight. Fifty-one per cent. were in females and forty-nine per cent.
in males.

Occurrence	No. of Cases 68	Hands 60	Feet 39	Face 37	Thorax 26	Abdomen 8
Sequence of onset .	47	. .	. .	. .	. .	. .
Appeared first in .	. .	35	10	0	1	0
Appeared second in	. .	6	12	10	2	1
Appeared third in .	. .	4	2	6	8	1
Appeared fourth in	. .	. .	. .	2	3	1

The hands were affected in 88 per cent. and affected first in 74.4
per cent. of the cases in all four types. In 40 cases where sensation
was mentioned there was no disturbance in 26. Perspiration was
absent in 3. There was no hypesthesia to touch, and pain in 3
and a hyperesthesia in 1. Temperature sense disturbed in 8. There
was only 1 case reported showing blood changes, a case having an
eosinophilia of 35.4 per cent., the polymorphonuclear leukocytic
count being 45.6 per cent.

Ulcers were present in 12 cases, over 50 per cent. occurring on
the distal portions of the extremities.

The thyroid was found unchanged in 12 cases, atrophic in 3, and
hypertrophic in 2.

Syphilis was negative in 13 cases and positive in 9, or 43.0 per
cent. Reynaud's disease was present in 4 cases, Addison's disease
in 1, tuberculosis in 2, and diabetes in 2.

It has quite generally been accepted that scleroderma is a tropho-
neurosis and due probably to a disturbance of the thyroid function.

Von Leube[27] first pointed out the coexistence of scleroderma
with Basedow's disease.

Osler, Grasset,[27] and Dehu,[27] from the changes in the nervous
system, the perversion of nutrition, analogous to that of myxedema,
together with Jeanselme, Singer, Hektoen, Leredde, Thomas and
others, regarded the cause as that of a thyroid deficiency.

In a series of 31 cases collected by Rocques, 22 showed abnor-
malities. But in our collected cases only 19 per cent. showed changes
in the thyroid. Because it was believed that this condition was due
to a thyroid deficiency, thyroid extract has been given and now is
generally given empirically. In 11 of the cases thyroid extract
alone was given. There was improvement in 2 cases, no improve-
ment in 4, and no change noted in 5 cases. Fibrolysin alone was
given in 1 case. Thyroid and fibrolysin were given in 1 case,
with no change noted. The other cases were treated with a variety

of drugs, and showed some improvement in 24 cases. No improvement in 13 and no change in 5. In order to observe the effect of thyroid extract not only upon the cutaneous manifestations of this disease but also on her metabolism, our patient was put on a constant diet, consisting of carbohydrates 200 gms., protein 75 gms., and fat q. s. to make 1600 calories. While on this diet the total nitrogen excreted in the urine was estimated every day and her blood-sugar and sugar tolerance determined.

After being on this diet for five days she was then given thyroid extract, gr. v, t. i. d., and the same observations were made.

The results show from the increased nitrogen elimination that the metabolism of protein was increased in her case, and may explain her temporary improvement as well as that of other patients on whom this drug has been exhibited.

The majority of cases followed after exposure, pyogenic infections, or were associated with a chronic debilitating disease. In general, after conditions which lower the vitality of the organism and interfere with metabolism.

The thyroid is not the only gland of internal secretion that is affected. Roux[27] found sclerotic changes in the hypophysis, and believed it to be a functional disturbance of that gland. Changes in the adrenals have been described. Dupre, Kahn, Rosch and others believed in a pluriglandular pathogenesis. Falta and Cassiver believe that in scleroderma the glands of internal secretion are affected, but the process is not primary in the ductless glandular system. Since all the glands of internal secretion may be affected in those having scleroderma, and since they are all probably influenced by the vegetative nervous system, it is possible that a disturbance of this nervous system may be the primary cause, though this has certainly not been proven.

Further evidence of a disturbance in the vegetative system is shown by the disturbance of the sweat glands, the trophic conditions, and vasomotor phenomena, as rush of blood to the head, transient areas of hyperemia, tachycardia, etc.

The following pathological findings show disease of this nervous system. Collier and Wilson[40] found that the cells of the intermedialateral tract were undergoing degeneration. The sympathetic fibers arise from these cells. Knapp[40] reported lesions found in the anterior horn of the cord. Brissaud[40] found changes in the cord about the ependyma.

Howell says the distribution of the lesions tends to be segmental. Hutchinson reports a case in which the distribution of the affected areas corresponds in distribution to that of the sympathetic from the fourth or fifth lumbar segment. Similar conditions are reported by Pringle and by Langley. Lichtwitz has observed degeneration of the chromaffin sympathetic ganglia in a case of scleroderma associated with Addison's disease.

We would also call attention to the changes found in the peripheral nerves in our case.

SUMMARY. Whether derangement of the nervous system be the etiological agent causing this disease we are, of course, unable to say. But having mentioned the findings of others, we will merely summarize and discuss the clinical data seen in our case.

We have to deal with a case of diffuse symmetrical scleroderma of the skin, the same, according to the patient, having begun on the distal extremities following an injury to the hip. While under observation she developed many of the characteristics of acrodermatitis chronica atrophicans (Herxheimer and Hartman, Wise), namely, the ulnar band. Anetodermie with softening of the skin over areas, which before had been hard and board-like in character. However, the patient has at all times had the most severe involvement of the skin in Scarpa's triangle, a portion of the body supposed to be immune to this disease.

Thus we find her to be a mixture of two types of scleroderma. From a search of the literature the same variability is found in many other cases, and while commending the attempt to classify the sclerodermas of the skin, we yet feel that this must be done along rather loose lines. They are quite apt to run over into each other and cause confusion if too narrow lines be drawn.

In this case there was marked improvement of protein metabolism as well as a clinical change for a time on giving her thyroid extract. We would call attention to the protein metabolism as a possible etiological factor in this disease. Moreover, there appeared to be some degenerative changes in the peripheral nerves of diseased areas.

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THE CURE OF PROLAPSE OF THE UTERUS.

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The diversity of opinions expressed in the writings of the modern authorities in regard to etiology and treatment of prolapse of the uterus led to a search of the older literature to see if a period

could be found in which there was a unanimity of thought on this subject. No such period was found; opinions were as diversified and debate as acrimonious a hundred years ago as they are today. In Dewees's *Diseases of Females*, published in 1837, we find a corroboration of this statement. At that period the profession was at loggerheads as to the value of conservative treatment, as instanced by the use of the pessary, astringent douches, astringent applications to the vagina, and the closure of the vagina by adhesions, from the use of caustics on the one hand and operative procedures on the other. Those who opposed the use of pessaries argued that the patients were not cured, that the conditions were made worse as the constant pressure of the passary caused ulceration and eventually cancer, and what seemed an unanswerable argument, that the pessaries caused so much pain that a woman would rather have her prolapse than a pessary. The operation proposed consisted in a denudation of the vulva with suture of the two sides together, so that the opening into the vagina was practically closed. If the operation proved successful then the patient was cured to the extent that the uterus could no longer project from the vagina. Dewees, an ardent advocate of the conservative treatment, gives in detail the method of treatment and recites the objections made against it. He then states: "So that my readers can form their own and unbiased opinion of the value of these two procedures, I will use Dr. F.'s own words in the description of this method." He then quotes Dr. Frick's description of the operation just outlined, and closes the chapter in this manner: "This horrible, severe, and ill-described operation is seriously proposed by Dr. F. as a substitute for the simple, successful, and easily managed pessary."

Diversity of opinion and acrimony in debate are not the only things common to the modern and older writers. Many of the views heralded as new were known years ago. "The ancients doubted the possibility of the uterus being entirely prolapsed on account of the strong support given by its ligaments. Now we scarcely attribute any retaining or holding power to the uterine ligaments. By experiments on the dead body, Professor Burns found that more resistance was afforded to procidentia by the connection of the uterus and vagina to the neighboring parts than by the agency of the ligaments; for although he cut the ligaments, he could not, without much force, make the uterus protrude. A debility and relaxation of the levator ani and perineal muscles, but particularly an extension and slacking of the pelvic fascia, in its connection with the uterus and vagina, are in a great measure essential to the production of the prolapsus." This might well have been written by the most modern advocate of the newer pelvic anatomy, but unfortunately for their priority in this field it is a quotation from Ashwell's *Diseases of Females*, published in 1845.

It may be of interest to review briefly the literature of this subject, showing the views held at different periods. Time will not permit a complete review, so I have divided the subject into ten-year periods, beginning with 1880. Apparently little progress was made in the treatment of prolapse from 1838 to 1880. Except for operations to repair the lacerated cervix and operations on the anterior wall of the vagina introduced by Marion Sims the treatment was practically the same. In Byford's book, published in 1881, are a number of illustrations of the most marvelous and deadly looking pessaries. He also discusses fully the pessary treatment, and expresses himself as favorable to their use. He also states: "An efficient use of astringents would appear in some cases of extreme prolapsus to be sufficient to effect a cure." In regard to surgery he remarks: "Surgeons have generally in their operation addressed themselves to but one item in the case. One party operates on the perineum, restoring or lengthening it, more or less completely to close up the vaginal orifice, while another party lessens the diameter of the vagina itself and condenses its walls into cicatricial or undistensible tissue." This latter was accomplished by the Sims operation or purse-string sutures without denudation.

T. Gaillard Thomas[1] records his method of treatment in a clinical lecture on a case of prolapse complicated by laceration of the cervix. The cervix was made and repaired, using silver wire. He proceeds: "The second step in the case will be the taking of a 'gore,' so to speak, in the anterior wall of the vagina by the operation known as elytrorrhaphy, and then the final operation will consist in the restoration of the destroyed perineum, after which I think the case can be discharged perfectly cured." He also records a second case[2] treated in the like manner. It is interesting to note that in the fifteen communications found in the *Index* for 1880, two dealt with urinary calculi as a complication of prolapse. The majority of the authors held that lacerations of the perineum was the most important etiological factor. W. V. Jackson,[3] however, makes this observation: "I have never seen a case caused by a ruptured perineum nor have I met with a case cured by sewing up such a laceration."

James P. Boyd[4] discussed the causes and treatment of prolapse. He noted that the condition at times appears in virgins. He gave as causes falls, torn perineum, and weight of uterus. His treatment consisted of pessaries, elytrorrhaphy, and narrowing of the vaginal orifice by extensive denudation and suture.

From the excerpts read it will be seen that the surgeons of 1880

[1] Boston Med. and Surg. Jour., October 27, 1881.
[2] Ibid., November 10, 1881.
[3] Australian Med. Jour., December 15, 1881.
[4] Med. Ann., Albany, July 1, 1881.

and 1881 had little concept of the pathological anatomy of the condition and little understanding of its rational treatment. Thomas was in advance of his confrères as an operating surgeon; he failed, though, to understand the anatomical injuries of lacerated perineum, cystocele, and prolapse. It seems odd that the surgeons of that period did not have a clearer understanding of the anatomical relationship of the bladder to the uterus and vagina. Vesico-vaginal fistulæ were more common then than now, as were also vesical calculi, and operations were frequent for the cure of these two conditions.

Ten years show a marked advance in the treatment of prolapse, and we find the surgeons in 1890 making use of the ligamentary supports of the uterus in attempts to effect a cure.

Smyley[5] said: "There are two types of cases, those due to relaxation of the pelvic peritoneum (meaning ligaments) and those due to relaxed and torn perineums." In the former he advised the use of the pessary and in the latter operation on the perineum. He advised Hegar's operation in old women and Martin's operation in women still in the child-bearing period. He reports a case of failure after a Hegar operation which was cured by an Alexander operation. He spoke of the difficulty of finding the ligaments in the inguinal canal, and reports that he practised on the cadaver before attempting the operation on the patient.

The use of the ligamentary supports was not in general use, however. B. C. Hirst[6] reported a case of complete prolapse in a girl, aged seventeen years. He cured the condition by performing a complete anterior colporrhaphy with sunken catgut sutures and by doing a posterior colporrhaphy somewhat after the method of Emmet.

That there was diversity of opinions at this period is shown in an article by I. B. Will.[7] He spoke of the chaotic condition of the subject, both from the stand-points of cause and cure. He said: "The theories advanced have been well-nigh innumerable and the treatment advanced ranging all the way from that of a Virginia physician who hung his negro patients head downward and poured the vagina full of a decoction of tan bark up to the most expensive silver and gold-plated utero-abdominal supports of modern times, on the one hand, and the narrowing of the vagina by plastic operations to the shortening of the round ligaments on the other." He also spoke of the diversity of opinion on the part of the faculty of the New York Polyclinic Medical School.

The treatment by pelvic massage, after the method of Thure Brandt, of Stockholm, was also in vogue at this period. The treat-

[5] Tr. Royal Acad. Med. in Ireland, 1889, vol. vii.
[6] Univ. Med. Mag., 1889–1890, p. 257.
[7] West. Med. Reporter, December, 1899.

ment was referred to by Alfred J. Smith.[8] The technic of this treatment consists in:

1. Lifting the uterus.
2. Massage of the uterus and its ligaments.
3. Forced separation and forced closure of the knees.
4. In tapotement of the lumbar and sacral vertebra.

The treatment of Thure Brandt has been recently recommended by Boldt, of New York.

In 1900 we find a still further advance in the treatment of prolapse. Watkins[9] discussed methods of treatment in vogue at this time. He considered them under the following heads:

1. Plastic vaginal operations.
2. Plastic vaginal operations combined with abdominal suspension.
3. Hysterectomy.

He then describes his method of operating, which was essentially a vaginal fixation of the uterus. Watkins has eventually developed this operation into one of the most important contributions on the subject of prolapse.

The first vaginal fixation was done by Schucking[10] in 1888. He performed the operation without freeing the bladder from the uterus. The bladder was frequently injured, and his work received little notice. Sanger,[11] in 1888, also described vaginal fixation of the uterus. The operation was also described by Mackenrodt[12] in 1892; Duhrssen[13] in the same year; and by Kuster[14] in 1894. Vaginal suspension was proposed by Vineberg[15] in 1896 and also by Wertheim[16] in the same year. These prior operations had to do with the correction of retrodisplacement of the uterus, and Watkins was the first to make use of the principle for the cure of prolapse. With the development of the method to the present interposition operation are associated the name of Frend, Duhrssen, Schanta and Wertheim.

Gynecologists were not all in accord with Watkins; in fact, it is only during the past few years that his operation has received the attention it deserves. John B. Deaver[17] said: "Three indications are to be met with, as a rule: the vaginal canal and vulva outlet must be restored to their normal condition, the enlarged or subinvoluted uterus corrected, and the uterine support applied from above." He favored ventral fixation, as sufficient support could not be obtained from the ligaments, and advised against vaginal hysterectomy.

[8] Tr. Royal Acad. Med. in Ireland, 1899, vii, 254.
[9] Am. Gynec. and Obst. Jour., 1899, xvi, 420.
[10] Centralbl. f. Gynäk., 1888, No. 12.   [11] Ibid., No. 2, p. 34.
[12] Berlin, Gynec. Sec., May 27, 1892.   [13] Centralbl. f. Gynäk., 1892.
[14] Deutsch. med. Wchnschr., 1894, No. 19.
[15] Med. News, March 14, 1896, p. 288.
[16] Centralbl. f. Gynäk., March 7, 1896.   [17] Am. Jour. Obst., 1900, xli, 478.

Smith,[18] however, advised vaginal hysterectomy, followed by plastic work for prolapse in elderly women. Werder[19] spoke against hysterectomy. He operated as follows:

1. Currettement of the uterus.
2. Amputation of the cervix.
3. Anterior colporrhaphy.
4. Ventral fixation of the uterus.
5. Colporrhaphy.

E. E. Montgomery[20] in discussing Werder's paper suggested shortening of the uterosacral ligaments.

Noble[21] thought the most important part of the operation for the cure of prolapse was the restoration of the perineum.

Fritsch[22] proposed a unique operation. He anteverted the uterus through an anterior vaginal section, brought the fundus down into the vagina and sutured the body of the uterus both to the anterior and posterior vaginal walls. The uterus became a permanent pessary in the vagina.

Here again in this period we see the diversity of opinion as to methods of cure. Marked advance, however, in certain aspects of the cure were made, the realization of the importance of the cystocele and rational methods for its cure proposed by Watkins[23] and Hadra[24] being probably the most important. The realization of the importance of the pelvic fascia as a support of the uterus and the suggestion of Montgomery for the utilization of the uterosacral ligaments were also noteworthy developments. All the radical operations proposed at this period for the cure of prolapse rendered subsequent pregnancy dangerous and sterilization had to be performed in the child-bearing woman.

The literature on this subject from 1900 to the present time is so voluminous that it is practically impossible to review it. Probably the most important papers are those dealing with the anatomy of the pelvis. Of these may be mentioned the description of the ligamentum transversus coli by Mackenrodt, papers by Jellett,[25] Tweedy,[26] Keyes,[27] Williams,[28] Keyes,[29] and Fitzgibbon.[30] Many communications have been presented dealing with the operative cure of prolapse. Of the most important are the various papers of Goffe, dealing with suspension of the bladder as a cure for cystocele and his operation of vaginal shortening of the round ligaments and also vaginal hysterectomy combined with his operation of

[18] Ann. Gynec. and Pediat., 1900, xiii, 813.
[19] Am. Gynec. and Obst. Jour., 1900, xvi, 13.   [20] Ibid.
[21] Ibid.   [22] Centralbl. f. Gynäk., 1900, xxiv, 49.
[23] Loc. cit.   [24] Am. Jour. Obst., 1889, xxii, 470.
[25] Jour. Obst. and Gynec. Brit. Emp., 1912, xxi.   Med. Press and Circ., London, 1914, ii.
[26] Jour. Obst. and Gynec. Brit. Emp., 1912, xxi.
[27] Am. Jour. Obst., September, 1913.   [28] Ibid., April, 1915   [29] Ibid., October, 1915.
[30] Surg., Gynec. and Obst., July, 1916.

bladder suspension for the cure of prolapse. Also important were those of Alexandroff[31] and Tweedy[32] dealing with Mackenrodt's ligament for the cure of prolapse; of Jellet[33] on the shortening of the uterosacral ligaments; the perfection of the interposition operation by Watkins and other authors; ventral fixation by Harris, Murphy, Baldy and Kocher, and the Mayo interposition of the broad ligaments.

In spite of the immense amount of careful work done on the anatomy of the pelvis in relation to uterine prolapse, the casual reader is left in a quandary on account of the many diversified opinions as to the value of the supportive power of the various pelvic tissues. For instance, some authors hold that the pelvic floor is all important, others that it gives absolutely no support; others that the uterosacral ligaments are most important, others that they are of no importance; others that the endopelvic fascia is all important, others that it is of no importance; still others that Mackenrodt's ligament is the true support, others that it plays no part in the support; others that the round ligaments have an important function, others that they are useless, and so on *ad infinitum*. The same is true of operative procedures. There has never been in the entire history of uterine prolapse such a diversity of opinion as to etiology and treatment as at the present time.

Much of the confusion results from the idealistic attempts to reach perfection. Some authors consider uterine prolapse a hernia and then proceed not to apply the principles of repair of hernia in other parts of the body. Others dilate on the anatomy of the pelvis and discuss altered anatomical relations and then attempt to restore normal anatomical conditions. This cannot be done; there never has or probably never will be, unless man is given the power of recreation, an operation that will restore either a lacerated perineum or a displaced uterus by restoration of normal anatomy. The utilization of anatomical supports, yes, but not restoration of normal anatomy. As a matter of fact, many of the operations based on the so-called restoration of the normal anatomy depend for their success by distortion of the normal anatomical supports. There is no reason why in some cases even that the adventitious supports should not be used to cure prolapse if success can be obtained. No one hesitates to restore a displaced kidney, stomach, colon, or liver by makeshift supports, and we hear nothing of restoring anatomical supports to these organs. We are satisfied if the means used hold the organs in place and cure the principal symptoms and produce no troublesome new symptoms. Why not apply the same principles to the cure of prolapse of the uterus.

Prolapse of the uterus is an abnormal condition, and in that sense a disease, and must be treated as conservatively or as ruthlessly as

[31] Zentralbl. f. Gynäk., Leipzig., 1903, xxvii, 762.
[32] Loc. cit.   [33] Loc. cit.

any other diseased organs as the nature of the individual case demands. As a matter of fact, we now have various ways of treating these cases successfully. No one method can be applied to every case, and while we can understand the enthusiasm of the promoter of an operation, for this method it is folly to attempt it.

In treating prolapse of the uterus we must understand the problems to be met in the individual case. What are the conditions which confront us?

1. In all cases of complete prolapse, there is present cystocele-rectocele and prolapse of the uterus. Usually other complications are present, such as endometritis, laceration of the cervix, hypertrophy of the cervix, enlargement or atrophy of the uterus, ulceration of the cervix, and ulceration of the vaginal mucous membrane.

2. Is the prolapse in a multiparous or nulliparous woman?

3. Is the prolapse in a woman before or after the menopause?

4. What is the operative resistance in the patient?

Let us first discuss conditions two and three.

On general principles no operation should be performed on the nulliparous woman in early life that would interfere with or complicate pregnancy or labor. On the other hand, conditions might be such that no such method would suffice to effect a cure. Under such circumstances we would be justified in performing an operation to effect a cure and sacrificing her child-bearing function. The same question arises in the case of the multiparous woman in the child-bearing period, though the loss of function would likely not entail as great a sacrifice on the part of the woman.

This would rule out interposition operations, hysterectomy, all fixation operations, both vaginal and abdominal, unless artificial sterilization was performed at the same time. When it is decided to maintain child-bearing function a choice can be made from the following procedures: Replacement of the bladder by the Goffe method, restoration of the perineum combined with vaginal operations of the round ligaments by the method of Goffe, Vinberg, Wertheim, etc., or abdominal shortening of the round ligaments by any of the many methods or ventral suspension; or the vaginal or abdominal shortening of the uterosacral ligaments or the operation on the ligaments of Mackenrodt after the technic of Alexandroff and Tweedy. If circumstances are present that these operations would not effect a cure, we can then resort to the interposition operation of Watkins, the Mayo operation, Goffe's operation No. 2, vaginal fixation, or abdominal fixation after the methods of Harris, Murphy or Baldy, etc., combined with the necessary plastic work and artificial sterilization. When sterilization is necessary and the uterus is not removed, both Fallopian tubes should be taken out in their entirety. I cannot see what is to be gained by removing a wedge from the cornua of the uterus, cutting out a portion of the tube and burying the end that is left

between the layers of the broad ligament except to complicate the operation.

Women before the menopause present, in addition to that of child-bearing, the question of drainage of menstrual and other uterine discharges. In the still menstruating woman no operation should be performed that will interfere with the drainage of the uterus. This rules out to a great extent the interposition operation, but leaves available all the other procedures subject to the considerations discussed in relation to child-bearing. In the woman after the menopause, none of these restrictions have to be considered and leaves available the operation best suited to the individual case.

Complications found associated with prolapse: Of these the most important is cystocele. Procedures for the cure of the cystocele are just as important as the cure of the prolapse itself. Simple denudation of the anterior vaginal wall is not sufficient to cure cystocele. The interposition operation of Mayo and Watkins in properly selected cases will almost invariably cure the cystocele, while at the same time curing the prolapse. The Goffe operation of suspension of the bladder at a higher level on the uterus or united broad ligaments, with anterior colporrhaphy should form an integral part of all other operative procedures.

Rectocele. An efficient operation for the restoration of the perineum should be performed. Personally, I favor a flap-splitting operation with suture of the levator ani muscles and fascia in the midline between the vagina and the rectum with elevation of the rectum after the method of Ward. A well-performed Emmet or Hirst operation will be just as efficient.

Lacerations of the Cervix. The cervix if lacerated should be repaired or amputated, depending on local conditions present, if the uterus is not to be removed.

Endometritis is present in nearly all cases except in those occurring in women after the menopause. When present the uterus should be curetted or else swabbed out with full strength tincture of iodine.

Ulcerations of the Cervix and Vagina. Unless amputation of the cervix or hysterectomy is to be performed, ulcers of the cervix should be treated and cured before resorting to any operative procedure for the cure of the prolapse. Ulcers of the cervix in women near and after the menopause may be a serious menace as to cancer, and hysterectomy is advisable in women at these periods when the ulcers fail to heal promptly under appropriate treatment. A recent experience of my assistant, Dr. Morrison, has led me to the belief that all cases of indolent ulcer of the cervix complicating prolapse should be examined microscopically before resorting to any operation which does not remove the uterus. He performed a Mayo operation on a woman in the early forties, an apparently

benign ulcer of the cervix was present. Microscopic examination of the specimen showed cancer at the site of ulceration.

When the vagina is ulcerated the ulcers should be cured before operating unless they are so situated that the vaginal denudation will remove them. Hypertrophy of the cervix should be treated by amputation.

Enlargement of the uterus may influence the type of operation to be selected. If enlargement of the uterus be present it should be treated either by complete vaginal hysterectomy, supravaginal hysterectomy by the vaginal or abdominal routes, or by removing a wedge-shape piece from the body of the uterus. When enlargement of the uterus complicates the prolapse the following operations are available: Vaginal hysterectomy followed by the technic of Goffe or Mayo; Watkins interposition operation with reduction of size of the uterus by removing a wedge-shaped piece of the body; supravaginal hysterectomy followed by the Baldy technic of ventral fixation of the cervical stump; Murphy's method of ventral fixation after removing a wedge from the body of the uterus.

Atrophy of Uterus. When the uterus is atrophic, none of the operations upon the various ligaments are likely to prove successful. The Watkins interposition operation is also contra-indicated when the uterus is small. Fixation of the uterus also frequently fails under these circumstances. The best results are probably obtained by the Mayo or Goffe operation. Conditions are such, however, at times that nothing short of obliteration of the vagina will affect a cure.

What is the operative resistance of the patient? The choice of operative procedure will depend upon the condition of the patient. In general, patients with prolapse have lowered tissue tone and are not particularly good surgical risks. On account of the extensive plastic work necessary, operations for the cure of prolapse take a considerable time to perform. Many of the patients are advanced in years and the use of ether and chloroform entail serious dangers to the operations. In the majority of our cases we operate under scopolamin-morphin narcosis alone or with a minimum amount of ether or chloroform, or else under spinal anesthesia.

Vaginal operations, as a rule, are safer than abdominal ones. Some cases, however, are such poor surgical risks that the vaginal operations necessary to effect a cure are contra-indicated on account of the length of time it takes to perform them. In these cases we have resorted to simply doing a high fixation of the uterus under local anesthesia. Of course the cystocele and rectocele are not entirely cured, but the patients are made much more comfortable, inasmuch as a large mass no longer projects from the vagina.

Finally, in those cases which for any reason cannot be operated on we have a very efficient method of treatment in the use of the Menge pessary.

GASTRIC POLYPOSIS.[1]

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Gastric polyposis is a sufficiently rare disease to be of considerable interest. During the past year 2 cases of this affection and an unusual specimen have come under our observation which we wish to report briefly.

Case I.—G.C.D., male, aged fifty-five years, admitted to the Union Protestant Infirmary November 1, 1915, complaining of weakness, anemia, and loss of flesh. Three months before admission the patient was suddenly taken with a severe chill followed by fever. A blood examination revealed malarial parasites, for which quinin was administered. The patient had lost twelve pounds in weight during the last three months. He had no pain, no digestive disturbance, but occasionally felt some discomfort in the lower abdomen. The bowels were regular but the stools were continuously tar-colored.

Physical examination revealed a well-developed, well-nourished man. The skin and mucous membranes are decidedly pale. There is no jaundice. The lungs and heart are normal. The abdomen is soft; there is no tenderness anywhere; no rigidity; no masses; no free fluid in the abdomen. The edge of the liver is palpable; there are no enlarged glands. The contents of the stomach obtained after a test meal contained considerable mucus, and there was an entire absence of free HCl, with a total acidity of 4, and an absence of lactic acid. A retention meal failed to reveal any evidence of the rice taken the evening before. The stools are dark in color and contain large quantities of occult blood. The blood examination reveals a marked secondary anemia, presenting 2,200,000 red cells; the hemoglobin varies between 37 and 55 per cent.

The roentgen-ray examination with a bismuth meal presents a cow-horn stomach of normal size with a very large, persistent filling defect at the junction of the greater curvature and pylorus; there is no obstruction.

On account of the constant bleeding, which was at all times revealed in the stools, the absence of free HCl in the gastric contents, together with a very large and constant filling defect as revealed by the roentgen-ray, the diagnosis of carcinoma of the stomach was

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made, notwithstanding the fact that the patient had lost but little flesh and had no pain or gastric disturbance.

Operation was advised and was performed November 18, 1915. Upon opening the abdomen a soft tumor, the size of a hen's egg, was palpated on the greater curvature of the stomach near the pylorus. An incision was made on the anterior wall of the stomach and a papillomatous mass with a broad base was observed springing from the posterior wall near the greater curvature. The surface was rough, ulcerated, and hemorrhagic, with numerous papillæ; it was about 7 cm. long, 4 cm. wide, and 5 cm. high. No other tumors were observed in the stomach. The tumor was excised with the electric cautery by making an oval incision around the base, including a good margin of normal tissue.

The patient made a rather uneventful recovery from the operation, but the stools continued to present occult blood. The hemoglobin was constantly low.
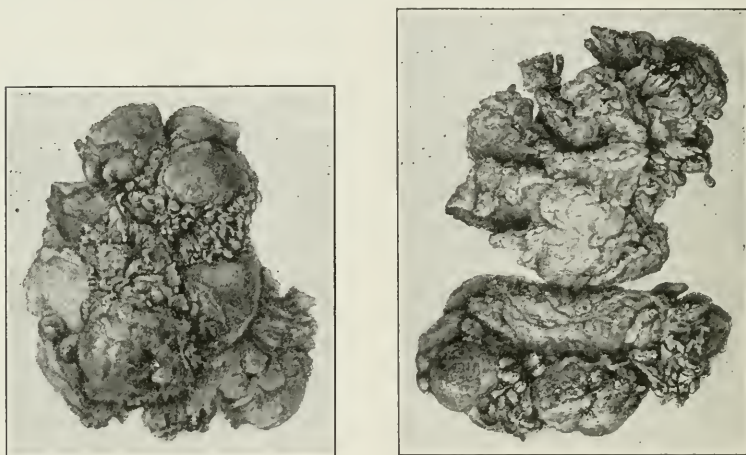
Fig. 1.—Case I.

The pathological report of the growth indicated that it was an adenopapilloma. Cancerous changes were revealed in the base of the growth.

Inasmuch as the patient's general condition did not improve and his anemia continued to increase, as well as on account of the constant appearance of blood in the stools even after numerous transfusions, further exploration was decided upon.

The operation was performed April 6, 1916. The stomach was found in good condition. The duodenum was found adherent to a mass posteriorly, which had apparently eroded into the duodenum. The mass was about the size of a hen's egg and densely

adherent to the abdominal aorta and vena cava. Numerous palpable glands were felt throughout this region. The mass was definitely malignant and its removal impossible. The patient recovered from the operation, but the anemia became more progressive and the stools continued to reveal blood.

Notwithstanding numerous treatments with radium the patient continued to loose flesh and strength, and died of exhaustion October 2, 1916.

Case II.—G. T. T., aged fifty years, was admitted to the Union Protestant Infirmary March 23, 1916, with a history of indigestion, with which he was first affected nine months ago. There was present pain, fulness, nausea, and vomiting. He had lost twenty-five pounds in weight. There was no history of hematemesis or melena.

On examination the patient is found poorly developed and undernourished. The liver is somewhat enlarged. In the epigastrium there is a sausage-shaped mass moving with the respiration and not tender to pressure. A radiographic examination reveals a large filling defect of a crater-like appearance at the pylorus, indicating an annular carcinoma of the pyloric ring; there is also marked retention (twelve hours). The gastric contents is brownish in character, containing mucus and blood presenting an absence of free HCl, but with a marked lactic acid reaction. The retention meal is positive; the stools contain blood.

A diagnosis of pyloric carcinoma with stenosis was made and operation advised. This was performed by Dr. Chaffee, resident surgeon of the Union Protestant Infirmary, March 26, 1916. On opening the abdomen a large mass presented itself at the pylorus. The tissue was hard and did not give the impression of being carcinomatous, but one enlarged gland was observed. A resection of the stomach containing the mass was made and a posterior gastroenterostomy performed. The patient made a satisfactory recovery.

On incising the resected mass a papilloma revealed itself just within the pylorus, projecting into the lumen so as to nearly occlude the orifice. The base of the growth is hard, indurated, and 3 cm. in diameter; that portion of the papilloma projecting into the pylorus is much softer and is 3 cm. in length. The sections made from the polyp present the typical appearances of malignancy. The carcinoma is of the medullary type in the papilloma and the scirrhus type in the stomach wall.

Of interest in this connection is a specimen found in the museum of the College of Physicians and Surgeons of Baltimore, presenting a typical example of multiple papilloma involving almost the entire stomach. It is interesting to note that that portion involving the pylorus has undergone a malignant degeneration.

A most exhaustive study of gastric adenopapillomata was published by Epstein in 1864, in which he collected 14 cases in 600

autopsies; he also collected 8 other cases from literature. Of these 22 cases 12 are solitary and the other 10 consisted of 9 small and 1 large polyp.

As regards etiology, most authorities point to a chronic gastritis as an underlying factor in the production of gastric adeno-papillomata. The disease is more apt to occur in males than females, and in most instances after the fortieth year of life.

Fig. 2.—Case II.

There are great variations as to the number of polypi that may be present, varying in individual cases from 100 to 200. They may also vary as to size from that of a pea to a hazel-nut, and may be as much as 2 or 3 cm. in length. They usually present a reddish or grayish aspect and are rather soft in consistency.

They are frequently pedunculated or attached by broad bases, or often club-shaped or cylindrical and frequently pigmented, the color depending upon the degree of vascularity. These growths may take their origin from any part of the gastric mucous membrane, the membrane covering them being smooth or villous.

The usual location of the growths is at the pylorus, although any portion of the stomach may be involved.

According to Menetrier there are two distinct types of gastric polyps depending upon whether the hypertrophy and hyperplasia involve the excretory or the deeper portions of the tubular glands. In the first type lobulation is more apparent and cystic forms are more common, the orifices of the excretory ducts being obliterated by the growth of the interglandular connective tissue. In the second type, those in which the deeper portions of the glands are
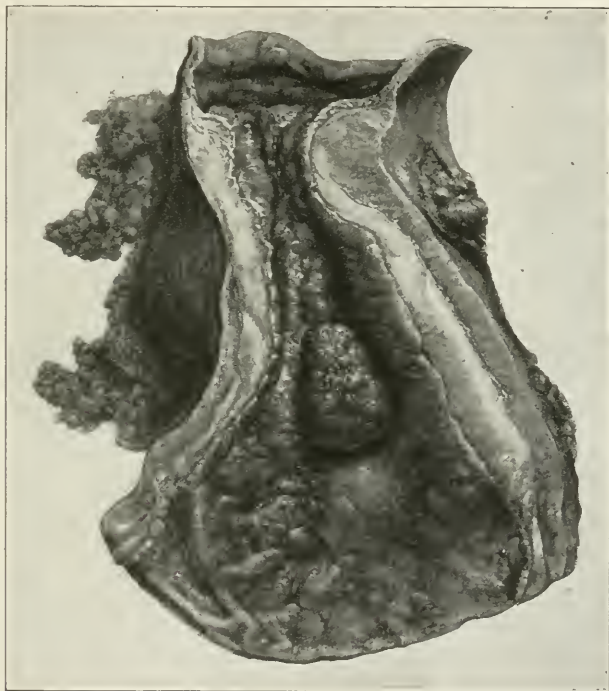
Fig. 3.—Case II.   Specimen in museum of College of Physicians and Surgeons, Baltimore.

involved, the polyps are uniform and tubulation is less pronounced. Between the two forms of polyadenomata there are a number of intermediate types; these mixed types are most common.

The mucous membrane not involved in the disease may present the appearance of a chronic gastritis. It may be congested, presenting hemorrhagic erosions with pigmentation. The polyadenoma "en nappe" of Menetrier is much less common. In this variety the hypertrophy and hyperplasia involve the entire mucous membrane in a certain area, thus developing into large plaques, and not as simple polypoid vegetations.

Microscopically polyps consist, according to Meyer, of hypertrophied mucous membrane muscularis mucosa and a connective-tissue core containing fairly large bloodvessels. The polyp presents on section three lobules, each of which contains a part of the core, here consisting of connective tissue and muscularis mucosa. The hypertrophied mucous membrane contains enlarged glands with dilated lumens. The glands are surrounded with columnar cells with basal nuclei; a large number of goblet cells are present, secreting mucus into the lumen of the gland. The interstitial tissue between the glands contains lymphoid cells, plasma cells, eosinophiles, and polynuclear leukocytes.

Inasmuch as polypi of the stomach are usually benign in character they may be present for a long period of time without producing symptoms. In fact, this affection is most frequently so obscure that a correct diagnosis is only revealed at operation or at autopsy. In some instances the symptoms are extremely severe; there may be present intense anorexia, edema, and ascites, producing a symptom-complex much like that of cirrhosis of the liver. Occasionally a diagnosis is made possible by the finding of a fragment of a polyp in the wash-water during lavage, such as was observed in Meyer's case, and at times by the presence of a large polyp in the stools. In the extensive forms of gastric polyadenoma, roentgenray examination is often very conclusive. There is, according to Meyer, a "mottled appearance of the entire right half of the stomach as if the bismuth were trickling through and around numerous masses together with the irregular and indefinite outline of the stomach." The condition may be mistaken for an achylia gastrica, inasmuch as polyps of the stomach are usually associated with absence of gastric secretion; the great excess of mucus, however, together with the unusual character of the mucus, of the peculiar egg-white appearance, distinguish this condition from an achylia gastrica. A most important and constant finding, too, is the presence of fresh blood appearing constantly in the gastric contents, especially, as Meyer points out, when observed in cases of achylia gastrica with normal or increased gastric motility, inasmuch as in those cases of hemorrhage due to ulcer there is usually hyperacidity with diminished motility.

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ETIOLOGY AND TREATMENT OF HEMORRHAGIC DISEASES.

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THE group of hemorrhagic diseases is a heterogeneous one comprising a number of conditions of very diverse pathogenesis. For practical purposes it has been the custom of clinicians to include in this group not only those diseases, such as hemophilia and the purpuras, in which a tendency to uncontrollable hemorrhage is the essential clinical manifestation of the disease, but also many dissimilar conditions in which a hemorrhagic tendency may be observed at some stage in the course of the disease. To this secondary group belong aplastic anemias, the leukemias, hepatic disease, and some of the infections and intoxications.

During the past few years the pathogenesis of the hemorrhages in this diverse disease group has been the subject of active study both in laboratory and clinic. This work has pointed the way toward a more logical classification of the various types of hemorrhagic disease, and much of value has been learned concerning their points of difference. The great advances which have been made in this direction are due in great measure to a change in our view-point regarding the relative importance of structural and of physiological pathology in the search for the causes of disease; and I believe that we owe in large part the additions which have been made in the past decade to our knowledge of the pathogenesis of the hemorrhagic group of diseases to an abandonment of the search for abnormal structure and to the vigorous application of biochemical and biophysical methods to the problem of blood coagulation in health and in disease.

Although it may be premature to speak of an etiological classification of hemorrhagic diseases, it cannot fail to be helpful to student, physician, and original investigator alike to take stock of what has been accomplished toward such a classification and to indicate how the results of these studies may be of help in diagnosis and in the formulation of a more rational and a more critical therapy.

Those who may be familiar with the literature on blood coagulation will know perhaps that not all of the elements concerned in clotting of normal blood are clearly understood. In fact, the theories of blood coagulation advanced by various workers differ widely both as to the number of factors which enter into the process as well as in the manner in which they act. It must be clear therefore that this uncertainty concerning the normal process of blood coagulation would lead to many divergent views regarding the forces at work in the coagulation of abnormal or pathological blood.

The theories given to explain the clotting of normal blood are many and intricate. One could hardly attempt to present them adequately within narrow compass. It is, however, essential to a clear understanding of the deviations from the normal which may occur in disease to have clearly in mind a few facts which have some basis in experiment. The theory of Howell satisfies the known facts of coagulation better than any other view thus far advanced, and we may accept his theory as a working hypothesis until further experiment has shown it to be untenable.

According to Howell there are five factors concerned in the clotting of normal blood—prothrombin, antithrombin, thromboplastin, fibrinogen, and calcium. All of these elements except thromboplastin are present in circulating blood. Within the blood-vessels prothrombin is held in combination with antithrombin and intravascular clotting is thereby prevented. When, however, blood is shed the antithrombin is neutralized by the thromboplastic substance of the tissue juices (blood cells, endothelial cells, platelets,

etc.). The liberated prothrombin is now activated by the calcium, and the thrombin which results converts soluble fibrinogen into the insoluble fibrin or the clot.

THEORY OF COAGULATION (after HOWELL)
A..CIRCULATING BLOOD   B..COAGULATING BLOOD
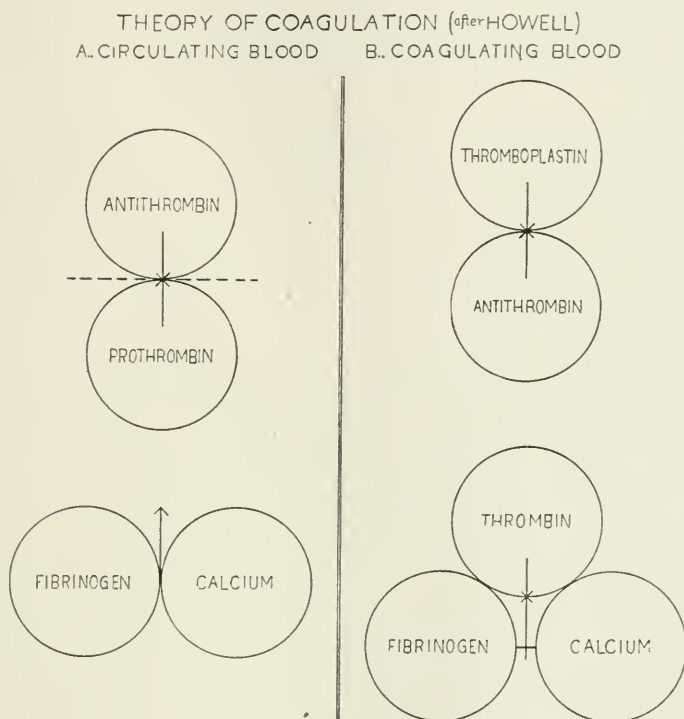
For purposes of clearness I have given a diagrammatic presentation of the conditions as we now know them to exist in the circulating blood and in the blood when it clots. It must be kept in mind, however, that such diagrams help only to visualize the process. They do not, of course, tell us the true nature of the phenomena concerned any more than graphic presentations of Ehrlich's side-chain theory tell us about the fundamental basis of infection and immunity.

This view of Howell has been the outcome of experiment and of the development of new methods of study. It is full of promise of applications in clinical work, both diagnostic and therapeutic. Already the use of his methods has made possible the classification of some of the conditions of this heterogeneous group on the basis of a defect in one or another element concerned in the clotting of normal blood. But before proceeding to a discussion of the results of such studies, it may be well to outline briefly the useful clinical methods which are now available for studying the pathogenesis

of the various types of hemorrhagic disease. These methods should be employed by anyone who would gain a better knowledge of the defect present in the condition studied or who would desire to have a better basis for instituting rational therapy. These methods are now sufficiently simple to be of value in the hands of clinicians not possessed of extensive laboratory equipment, and surely all practical workers in hematology cannot afford to be without a knowledge of them.

METHODS OF STUDY. 1. *Determination of the Coagulation Time.* It is not necessary to review at this time the numerous methods which have been recommended for the determination of the coagulation time. I wish simply to call attention to several requirements which must be complied with if the results obtained are to be reliable. In the first place all specimens of blood obtained for a determination of coagulation time should be as free as possible from admixture with tissue juices, and secondly a comparison should always be made in each instance with a specimen of blood taken from a normal individual with the same precautions. Judged by these criteria the methods of determining blood coagulability by skin puncture are unreliable and should be discarded. Probably the most accurate method thus far available is that recommended by Howell. This worker aspirates blood directly from the median basilic vein into a syringe coated on the inside with a thin layer of a petrolatum-ether mixture. Two c.c. are immediately expelled into a wide tube, about 21 mm. in diameter (the test-tubes ordinarily used in bacteriological laboratories serve well for this purpose), which has been especially cleaned with a bichromate acid mixture. The period elapsing between the moment the blood is drawn and the moment at which an invertible clot has formed is regarded as the coagulation time. By this method the coagulation time of normal blood averages about twenty minutes. Reliable results are obtained only when the needle of the syringe enters the vein readily and when there is a minimal amount of admixture with tissue juice.

2. *Determination of Bleeding Time.* According to Duke the bleeding time is the tendency to bleed from a fresh cut. The duration of such a hemorrhage is determined by blotting upon absorbent paper all the blood which flows from a small incision at intervals of thirty seconds. Each drop will give in a rough way the volume of blood shed in the given time interval, and the total duration of such a hemorrhage will represent the bleeding time. The normal bleeding time varies from one to three minutes. It should be kept in mind that the bleeding time is independent of the coagulation time. A determination of the bleeding time yields information concerning not only the elements as they exist in the circulating blood, but also additional knowledge of value as regards the potency of the tissue juices, the mechanical and chemical action of the blood platelets, and the elasticity of the skin. Subsequently, in connection with a

discussion of the individual disease types, it will be pointed out that the bleeding time may be normal when the coagulation time is delayed, or the reverse. A knowledge of the bleeding time has been shown to be of value not only from a diagnostic view-point, but also from the stand-point of surgical interference. We believe it desirable that such knowledge should be obtained preliminary to any surgical operation on a patient in whom there may be a tendency to immediate hemorrhage from one cause or another.

3. *Retraction of the Clot and Enumeration of Blood Platelets.* Normally, a blood clot quickly retracts from the sides of the vessel in which it is contained and expresses serum. This phenomenon has been ascribed to the presence of the blood platelets, so that it is not surprising that a low platelet count and non-retractility of the clot are so frequently encountered in the same hemorrhagic condition. The presence or absence of clot retention is determined simply by incubating the clot at 37° C. for from twelve to twenty-four hours. For this purpose it is time-saving to use the same specimen employed for the determination of the coagulation time. In normal blood, retraction begins after several hours, and is complete within eighteen to twenty-four hours; in pathological blood, on the contrary, contraction may occur only after a long time or not at all.

For the enumeration of blood platelets a number of methods are available, but that of Wright and Kinnicutt[14] appears to have given the most reliable results in the hands of most workers. The method may be recommended because of its simplicity. It has now come into general use, and detailed descriptions of the technic will be found in recent editions of works on clinical pathology.

4. *Quantitation of Prothrombin and Fibrinogen.* Of the methods at present employed for a determination of the fibrin factors only two have reached the stage of simplicity which makes their use as clinical tests possible. An idea of the relative amount or relative strength of the prothrombin in the blood may be obtained by a simple method devised by Howell.[1] In this paper it will not be possible to enter into an explanation of the principles upon which the test is based. I shall merely outline the reaction as it is carried out in practice: To a series of tubes containing a constant amount of the oxalated plasma (1 part of 1 per cent. solution of sodium oxalate made up in 0.9 per cent. solution of sodium chloride to 9 parts of blood) is added dilute calcium chloride (0.5 per cent.), 1 drop to the first, 2 drops to the second, and so on up to 4 drops to the fourth tube. Coagulation will result and the time of coagulation as measured by the invertibility of the clot will be shortest in the tube containing the optimum amount of calcium. Tested by this method the clotting time of normal human blood averages about ten minutes; whereas the coagulation of pathological blood (hemophilia) may at times be delayed sixty minutes or more. This test, as will be pointed out later, gives a simple and reliable means of

diagnosing hemophilia *in vitro,* and we believe should be part of the routine examination of the blood in a patient presenting hemorrhagic symptoms.

Fibrinogen can be determined accurately only by gravimetric means. But this method is not suitable for clinical purposes. It is possible, however, to get a good idea of the fibrinogen content of the blood by an examination of the blood clots in a small test-tube, or better still, by clotting a little oxalated plasma by means of calcium, from which a rough estimation of the amount of fibrinogen is possible.

An accurate determination of antithrombin requires the preparation and use of pure solutions of thrombin and fibrinogen, a task beyond the scope of the clinical worker. Until some simpler technic can therefore be devised for quantitating this substance it will be necessary for the present to assume that an excess of antithrombin is responsible for a hemorrhagic condition only if the other factors have been shown to be present in normal amounts.

The calcium factor, too, may at the present time be neglected, for there is no evidence that any form of hemorrhage is referable to an abnormality in this element. In icterus, to be sure, bleeding may be attributable to an abnormality in calcium. It has been shown, however, that the blood calcium in this condition is not actually diminished in amount, but rather is bound by bile pigments, and therefore only slowly available for the requirements of coagulation. This functional deficiency of calcium in cholemia is simple to demonstrate by the "calcium *in vitro* test" of Lee and Vincent. This test is done in a simple control determination of the coagulation time by the use of a second determination with 3 drops of calcium chloride (1 per cent. solution) to 1 c.c. of blood or to 2 c.c., if the technic above described is followed. The addition of calcium will accelerate the clotting of blood from cases of obstructive jaundice, but will not influence control determinations similarly made on normal blood.

5. *Fibrinolysis.* Fibrin-dissolving ferments may be responsible for the hemorrhages in some cases. Even when the blood coagulates normally the clots are not permanent, and oozing may continue through the softened and dissolved clots which form at the site of injury. The presence or absence of fibrinolytic ferments can be detected by incubating the clot at body temperature and noting whether any dissolution occurs in a stated time interval. Since the clot from any specimen of blood will undergo a certain amount of dissolution if left in its serum a sufficient length of time, it is well to restrict the term pathological fibrinolysis to instances of complete clot dissolution occurring within twelve hours when the blood is kept at body temperature.

The Differential Diagnosis of Hemorrhagic Diseases Based upon a Study of the Blood. In gathering together the results of the numerous studies made upon some of the diseases of

Hemorrhagic diseases.	Coagulation time.	Bleeding time.	Number of platelets.	Retractility of clot.	Factors of coagulation.				Fibrino-lysis.	Remarks.
					Prothrombin.	Anti-thrombin.	Fibrinogen.	Calcium.		
Primary hemorrhagic disease. A. Hemophilia[1 2 3]*	Prolonged	Normal	Normal	Normal	Diminished	Relatively increased	Normal	Normal[5]	Negative	Demonstration of prothrombin deficiency is a reliable in vitro test for the diagnosis of the hemophilic condition.
B. Morbus maculosus neonatorum[6]	Prolonged	Normal	..	Normal	Diminished	Normal	Normal	Normal	..	
C. Purpura hemorrhagica[1 7]	Normal	Prolonged	Markedly diminished	Non-retractility of clot	Normal	Normal	Normal	..	..	Diminution in number of platelets and non-retractility of clot make diagnosis of purpura possible, even in absence of other features.
D. Chronic purpura[1 3 8]	Normal	May be prolonged	Diminished	Non-retractility of clot	Normal	Normal or increased	Normal	..	Negative	
Secondary hemorrhagic disease. 1 Blood diseases. A. Aplastic anemia[8 9]	Prolonged	Prolonged	Diminished	Diminished	Diminished	Normal or increased	Normal	..	..	Coagulation time and bleeding time both prolonged (compare with hemophilia).
B. Leukemia[3 8 9]	May be prolonged	Normal or prolonged	Normal or diminished	Normal or diminished	Normal	Increased	Slightly diminished	..	Negative or positive	Platelets diminished in lymphatic leukemia; increased in myeloid leukemia; fibrinolysis present in myeloid; absent in lymphatic leukemia.[10]
2. Hepatic disease. A. Cirrhosis of liver[8 11]	Normal	Prolonged	Normal	Normal	Normal	Normal	Diminished	Normal	Positive	The prolonged bleeding time in cirrhosis with hemorrhagic symptoms is due to the fibrinogen deficiency; the clot is too soft to close the ruptured vessels.
B. Cholemia obstructive (without liver injury)[3 12 13]	Normal or prolonged	Normal	Normal	..	Normal	Normal	Normal	Diminished	..	Blood calcium may be present in excess but it is bound by bile pigment and is unavailable for prothrombin activation.
C. Cholemia (with liver injury)[3 9]	Prolonged	Normal or prolonged	..	..	Normal or diminished	Increased	Normal or diminished	Normal	May be positive	Terminal drop in prothrombin noted in one instance;[9] prothrombin may be diminished in congenital family jaundice and in congenital stenosis of bile ducts.[3]
3. Infections and intoxications (symptomatic purpura): septicemia, typhoid, tuberculosis, chloroform poisoning[3 6 9]	Normal or prolonged	Normal or prolonged	Normal or slightly diminished	Normal	Normal or diminished	Increased	Normal or diminished	Normal	..	Bleeding time prolonged in chloroform poisoning due to fibrinogen deficiency; platelet count may be diminished during acute stage of infections;[7] prolonged coagulation time and bleeding in septicemia due to antithrombin excess.

* The numbers refer to the papers listed in the bibliography. The facts compiled in this table are based upon the data obtainable from these investigations.

this group by the methods outlined, I have endeavored to find out whether these could be differentiated one from the other by the *in vitro* tests without resorting to a differential diagnosis based upon clinical symptomatology. A glance at the tabulated results will show that such a laboratory diagnosis as opposed to a clinical diagnosis can readily be made in those disease types at least which most frequently come to the attention of the clinician. It is possible to group the diseases studied according to the essential abnormality in the coagulation complex, although it must be kept in mind that when carefully studied, some of the conditions under consideration may show a defect in more than a single factor of coagulation.

Platelet Group. Duke[7] in particular has emphasized the relationship of the blood platelets to hemorrhagic disease. And there can be little doubt that a diminution of these elements is directly responsible for the hemorrhages observed in purpura hemorrhagica and in some, but not all, types of chronic purpura. For thorough analyses of the blood, especially in purpura hemorrhagica, has shown the other factors of coagulation to be present in normal amounts. One might, of course, enter into a lengthy discussion concerning the manner in which platelets act in blood coagulation, but such speculations would lead one too far afield. Duke has laid emphasis upon the mechanical action of blood plates and their ability to stop hemorrhage by the role they play in the formation of thrombi. Others believe that platelets also facilitate clotting through their chemical action, for, as is well known, platelets are an important source of prothrombin and a thromboplastic substance which hastens coagulation by neutralizing the antithrombin present normally in the circulating blood. According to this view, platelets bear a more intimate relationship to the other factors concerned in blood coagulation. Doubtless both conceptions of the function of platelets is correct, and their importance rests both in their agglutinative power as well as in their content of prothrombin and thromboplastin.

It is well, then, to bear in mind that one type of hemorrhagic disease (acute and chronic idiopathic purpura hemorrhagica) may be attributed to an extreme reduction in the number of platelets. Furthermore, evidence that the platelets bear a direct relationship to the hemorrhages in this group comes from the observation that relief of the tendency to bleed follows not only the rise in the platelet count occurring at a remission of the disease, but following the increase in platelets brought about by transfusion. The value of transfusion in the treatment of the purpuric diseases will be considered in the paragraphs on treatment.

The prolonged bleeding time and non-retractility of the clot, which occur with such constancy in this group, are directly dependent upon the platelet deficiency. Only one other group of conditions shows so marked a prolongation of the bleeding time,

namely, the diseases associated with a reduced quantity of fibrinogen. In this instance prolonged bleeding is striking only if the reduction is extreme.

Prothrombin Group. The results of experimental and clinical studies obtained thus far give strong support of the existence of a group of conditions in which hemorrhage may be attributed to a deficiency of prothrombin. There can be little doubt that the hemophiliac condition, both in the true hereditary type of the disease and in those instances in which the disease arises *de novo* without a definite history of heredity, is due to diminution of this element. In fact, this property of hemophiliac blood is so striking that it distinguishes hemophilia at once from other hemorrhagic conditions and serves as a convenient method of making a diagnosis of hemophilia *in vitro* even in the absence of any proved history of the existence of the disease in the patient's antecedents.

In this same group belongs also hemorrhagic disease of the newborn (morbus maculosus neonatorum). Whipple has studied a type of this disease (melena neonatorum) in which there was a complete disappearance of prothrombin from the circulating blood. And more recently we have observed at the University of California Hospital an instance of hemorrhagic disease of the newborn with profuse bleeding from the umbilicus in which a similar defect was demonstrable.[4] There is some evidence that prothrombin may be present at birth but vanishes during the first few days of life.[15] It would seem that the function of the tissues and organs concerned with the elaboration of prothrombin in these cases is not yet in stable equilibrium, and this may account for the success following the intravenous injections of whole blood in tiding over a period of hemorrhage which would otherwise prove fatal.

In still another disease group—the aplastic anemias—the cause of the bleeding tendency is due in part at least to a prothrombin deficit. Unlike hemophilia and hemorrhagic disease of the newborn it has been possible to show that in aplastic anemia a diminution of the blood platelets is also an important cause of the hemorrhages. It is of interest that in this disease we have definite evidence of the existence of a hypofunctionating marrow, so that it may be contended that the aplastic marrow may be partly responsible for the lack of certain of the factors of coagulation. That this is true has been proved by recent experiments. Hurwitz and Drinker[16] have shown that coincident with the drop in blood platelets following marrow injury by benzol there is also a drop in circulating prothrombin, and more recently Drinker[17] has shown by actual profusion of the bone marrow that it contains prothrombin. It would appear, therefore, that the hemorrhagic features of the aplastic type of pernicious anemia are directly secondary to a definite deficiency of the bone marrow.

Antithrombin Group. This group consists of a number of heterogeneous clinical entities. Although it is permissible to place them under this heading, because an antithrombin excess is the chief cause of the pathological hemorrhages associated with these various diseases, it should be emphasized that this is not the only demonstrable defect in the coagulation elements. Thus certain chronic purpuras in which the hemorrhagic symptoms may be due to periods of antithrombin excess also show moderate diminution of blood platelets with the attendant phenomena of prolonged bleeding time and non-retractility of the clot. Of the other blood diseases, cases of aplastic anemia may at times show an excess of this element, although this was not true of the patient studied by us. The leukemia patients, too, have been shown to have an excess of antithrombin in their blood during the periods of active hemorrhage, but they also may have a deficiency in other factors—platelets or fibrinogen.

According to the best evidence, an excess of antithrombin may occur with greater constancy in diseases of the liver or in infections and intoxications producing liver injury. Thus far an antithrombin excess has been demonstrated to be the cause of hemorrhagic symptoms in icterus associated with liver injury. This is also true in certain cases of septicemia, typhoid fever, and miliary tuberculosis. These clinical observations confirm the experimental studies, which seem to indicate that the liver may be concerned with the production of antithrombin.

Fibrinogen and Fibrinolytic Group. Here belong, for the most part, those diseases associated with acute or chronic liver injury. The fibrinogen of the blood may be greatly reduced by various poisons, such as chloroform[13] and phosphorus, which injure the liver. In severe poisoning the fibrinogen may reach a very low level. A deficiency in this element explains the hemorrhagic features and the prolonged bleeding time of these intoxications. The blood coagulates, but the clots are too flabby to close the ruptured capillaries. Whipple believes that a similar explanation may be offered for the hemorrhagic tendency observed in acute yellow atrophy and in yellow fever.[15]

Of the chronic liver diseases which may show a low fibrinogen content of the blood, liver cirrhosis is the most important. It should be emphasized that a marked decrease of fibrinogen in this condition is not of constant occurrence, but when the content is low it is of grave prognostic import.

A ferment capable of giving rise to hemorrhagic symptoms by dissolving the fibrin of the clot has been demonstrated in liver diseases and more especially in hepatic cirrhosis with insufficiency. It has also been demonstrated in the blood of certain types of myeloid leukemia, and it has been suggested that its absence in the lymphatic type of leukemia may serve as a means of differentiating the two types *in vitro*.[10]

· *Calcium Group.*   Thus far no experimental proof has been brought forth that a deficiency in calcium salts is responsible for any form of hemorrhage.   It has already been pointed out that the prolonged coagulation time in obstructive jaundice without liver injury is not due to a diminution in the calcium content of the blood, but rather to its unavailability for coagulation.   From a practical view-point, however, an actual or a functional deficiency of calcium would lead to the same symptoms, and the therapeutic indications would therefore be the same.   These will be considered in the paragraphs on treatment.

Other Factors.   Only little work has as yet been done upon the significance of deficient thromboplastin formation.   Whether or not a deficiency in this substance may give rise to a hemorrhagic tendency is difficult to determine at present because no direct method of studying this factor exists.   Some information concerning this substance as it exists in the blood can be obtained by an enumeration of blood platelets.   But information obtained from this source is incomplete, inasmuch as all of the formed elements of the blood and other tissues have been shown to possess thromboplastic properties to a greater or less extent.   Sahli has indeed maintained that in hemophilia there exists a thromboplastin deficiency (fermentative inferiority) of the protoplasm of the body, whereas others have localized it partly in the blood platelets.[19]

THE TREATMENT OF HEMORRHAGIC DISEASES.   *General Treatment.*   Although one must admit that as regards a specific therapy the elaborate studies described have contributed little, they have, however, made possible a more rational and a more critical treatment of hemorrhagic conditions.   In the paragraphs on treatment I purpose to consider separately the principles underlying the general and local measures recommended, and of the former only those whose value has been tested by experiment.   Apart from all other considerations it seems fair to assume that a therapeutic measure employed for the general control of hemorrhage is successful only if it causes a cessation of the bleeding, and so affects the disease process itself that the coagulability of the blood is increased.   On the basis of such criteria only a few of the measures advocated can be said to possess real value.

Calcium Therapy.   Although clinical reports as to the value of this method of treatment have been conflicting, the general idea has been widely accepted that the coagulation time in disease can be shortened at will by giving the proper dose of calcium.   The great popularity which this form of treatment has received in the control of the hemorrhages of hemophilia and other bleeding conditions is largely due to the publications of Sir A. E. Wright.   He was among the first to call attention to the need of an accurate method of obtaining clinical data on blood coagulability as a rational basis of therapeutics in this group of diseases.   And by testing the

coagulation time with a series of capillary tubes before and after the ingestion of calcium salts, Wright arrived at the conclusion that calcium administered in repeated doses by mouth can render the blood more coagulable.

In general the contentions of Wright have not gained support from the work of later investigators. In 1909 Addis[20] by using a modification of McGowan's method of determining blood coagulability, reported a careful series of experiments on the effect of calcium salts on the blood in various types of disease. From these studies he concluded that calcium salts are unable to effect any change in the coagulation time of the blood. Indeed, all subsequent experimental as well as clinical observations have confirmed his findings so far as hemophilia is concerned. According to the best experimental work there is only one condition in which calcium feeding is indicated, namely, in obstructive jaundice with a delayed coagulability of the blood. Both Schloessmann[21] and very recently Lee and Vincent[13] have observed a shortening of the coagulation time following the administration of calcium in this condition. Lee and Vincent point out that to be effective calcium must be administered in large doses (100 grains a day), and must be given over a period of several days before any marked effect on the coagulation time is seen.

Serum Therapy. This form of treatment has gained remarkable popularity since Weil, in 1905, reported the successful therapeutic results following the use of serum in hemophilia. The author feels that while the question of the usefulness of serum or any other remedy for the constitutional treatment of these disorders must in a measure be determined on the basis of clinical results, that too little attention has been paid to the evidence gained from well-controlled experiment. Instead of narrating the clinical successes and failures which have attended the use of serum I prefer at this time to call attention to some observations and experiments concerning the use of serum which most clinicians and writers on this subject usually fail to mention.

The essential coagulation-accelerating substance contained in fresh serum is thrombin. In addition it may contain a small amount of thromboplastin, liberated by the disintegration of cellular elements, and some antithrombin which is present in small amounts in all sera and bloods. It should be emphasized that old serum differs markedly from fresh serum in the following respect: On standing a few days the thrombin of the serum is converted into an inactive form—metathrombin—so that old serum contains less thrombin and more antithrombin. Because of this transformation it can actually be shown by *in vitro* tests as well as by subcutaneous and intravenous injections into animals and man that old serum *retards* rather than *hastens* the clotting of blood not only in normal animals but also in pathological conditions like hemophilia.[21] On the basis of these experimental studies we believe that old serum—anti-

diphtheritic and the like so commonly employed in the treatment of hemorrhagic conditions—should be entirely discarded.

And if we adhere to the criteria which should guide our judgment as to the value of a therapeutic measure in checking constitutional hemorrhage it is not possible to make any greater claims for fresh serum. It is true that an extensive literature has accumulated in support of the usefulness of this measure in a host of conditions manifesting a bleeding tendency, but in only a few instances have the observations been controlled by studies upon the blood coagulability before and after the serum injections. In fact, where careful experiments to determine this point have been carried out they have demonstrated the lack of value even of fresh serum.

Concerning the value of serum in the disease groups which have been considered above, one may say with considerable certainty from the searching experiments of Schloessmann and a number of other workers (Sahli,[23] Baum,[24] and Ottenberg and Libman)[25] that serum injections have little if any effect on conditions due to a prothrombin deficiency, hemophilia, and hemorrhagic disease of the newborn. Schloessmann was able to show conclusively that no immediate or delayed increase in the coagulability of the blood resulted following the subcutaneous or intravenous injection of fresh serum into hemophilic patients. Nor has serum yielded brilliant results in the platelet group of diseases—the purpuras; whereas in them the use of whole blood has been of the greatest value in bringing hemorrhage to an early arrest. The reason for this will be discussed in the paragraphs on the therapeutic value of whole blood. Moreover, it is obvious that the use of serum would be valueless where the faulty coagulation depended upon an absence or a deficiency of fibrinogen, and that the use of old serum would be contra-indicated in the group in which the hemorrhagic tendencies were attributable to an excess of antithrombin. In fact, Howell has shown that following the intravenous injection of fresh serum or thrombin the antithrombin may even show an increase a few hours after such injections, although the balance quickly returns to normal.

In the light of these facts it is a little difficult to explain the enthusiastic claims which have been made for serum therapy in the literature. Doubtless serum does at times give remarkable hemostatic results in some cases of hemorrhage, and this is in harmony with the striking coagulation-accelerating action of serum on whole blood in the test-tube. The manner in which serum may produce such favorable results *in vivo* is as yet not clear, although it must be evident from what has been said that injections of serum do not increase the coagulability of the blood. And in fact the development of improved methods of administering whole blood in the treatment of hemorrhagic conditions and the brilliant results attending its use is gradually causing some of the enthusiasm for serotherapy to wane.

Whole Blood.. Obviously, the most ideal therapy would consist in supplying to the patient the element in which his blood is lacking, or in neutralizing those substances which may be present in excess. Unfortunately, such a mode of treatment is not possible in the present state of our knowledge. In the absence of a specific therapy the use of whole blood which contains all of the factors concerned in clotting appears to be most logical, and, in fact, remarkable success has attended its use in the hands of a large number of clinicians. It is not my intention to recount the numerous methods which have been advocated for the administration of whole blood, but to dwell rather upon the principles underlying this form of treatment.

The number of instances in which the use of whole blood has yielded brilliant therapeutic results have increased greatly during the past few years; but unfortunately only a few of the recent reports contain observations on the blood coagulability before and after such therapy, so that we do not know just how whole blood produces its favorable results. Those cases which have been studied from this view-point, however, have given us some interesting facts concerning the effect of whole blood upon the factors of coagulation in a few disease groups which, I believe, deserve brief consideration.

According to the clinical observations of Ottenberg and Libman, transfusion may be looked upon as a specific therapy for the control of the hemorrhages in hemophilia. In fact, they go so far as to recommend that "every individual known to have hemophilia ought to have at his command several persons whose blood by previous tests is known to be compatible with his . . . .[25] So far as the author is aware, experiments have not as yet made clear the reason for this specific action of whole blood in hemophilia. But a little insight into its probable action has been gained from experimental studies on the influence of blood in hemorrhagic disease of the newborn, which as has been pointed out also belongs to this group of conditions associated with a prothrombin deficit. In a case of hemorrhagic disease of the newborn, which recently came under our observation,[4] it was found by blood studies that the essential defect in the process of coagulation was due to a deficiency of prothrombin, which probably accounted for the excessive bleeding from the umbilicus. Having tried local hemostatics without good effect, resort was finally had to the injection of whole blood into the longitudinal sinus through the anterior fontanel. After the injection of 40 c.c. of blood the hemorrhage ceased almost instantly and a study of the blood about six hours later showed a normal coagulation time and a normal prothrombin content. This experience is cited in detail because we know from experiment that in this case a restoration of the prothrombin balance was effected, either by a stimulation of the tissues concerned with the elaboration of this

substance or by the actual addition of this substance to the circulating blood.

Furthermore, experiment has shown that transfusion of whole blood is also especially indicated in another clinical condition in which both the circulating prothrombin and the blood platelets are deficient, namely, aplastic anemia. Drinker and I[8] have followed such a case for over eight weeks. Each time following transfusion there was prompt cessation of bleeding from the gums, and, as studies of the patient's blood showed, there was also an increase in the platelet count and in the prothrombin. To be sure the improvement was only temporary, but the administration of whole blood tided the patient over the immediate dangers of prolonged hemorrhage.

In the platelet group of hemorrhagic conditions—the purpuric diseases—transfusion has been found to be the only logical method of combating hemorrhage. Transfusion of blood in this group of hemorrhagic diseases has been especially recommended by Duke.[7] This worker has shown by a study of the blood before and after transfusion that both the bleeding time and the number of platelets may become normal after this procedure. In two out of the three cases which he cites the platelet counts before transfusion were 3000 and 20,000; the bleeding times were respectively ninety and twenty minutes. After transfusion the counts were 110,000 and 89,000, and the bleeding time in each case was three minutes (normal). After the disappearance of these platelets, apparently introduced into the patients' circulation by transfusion, the bleeding times became forty and twenty minutes. But none of the patients showed so marked a tendency to bleed after transfusion as before, even after the platelet counts had dropped to their previous low level. It would appear, therefore, that platelets introduced into the blood stream in this way rapidly disappear. In these two instances there was complete relief from hemorrhage for three days after transfusion.

Ottenberg and Libman are equally enthusiastic over the therapeutic results of blood transfusion in purpura hemorrhagica. They report twelve transfusions in 9 patients, with complete recovery in 6 cases. Not only do they emphasize that transfusion produces a prompt cessation of the hemorrhages in most of these cases, but they believe that it also has some curative action, the exact nature of which is not entirely clear. That it has some connection with the fresh supply of blood platelets seems likely, but all the benefits produced cannot be accounted for in this way, for the normal life duration of platelets is known to be very short. It is not unlikely that some of the favorable action of whole blood may be attributed to the effect which it may have in stimulating the regeneration of thromboplastic substances (platelets). This view has some basis in experience because, as Emsheimer[26] and others have found, small

intramuscular injections of whole blood in purpura hemorrhagica are as efficient in controlling bleeding as are large transfusions, and it cannot be assumed that small intramuscular injections exert their influence by direct action.

Other Measures. There is one other form of general treatment which has been subjected to experimental study, and which therefore deserves brief mention. Some workers, especially Schloessmann,[21] have tested the effect of intravenous injections of saline extracts in hemophilia, and Hurwitz and Lucas[2] have made observations upon the effect of intramuscular injections of the brain phosphatid— *kephalin* on the coagulability of the blood in hemophilia. All of these studies have demonstrated the ineffectiveness of this form of therapy. The reason for these failures is not far to seek. As Howell has shown, solutions of pure thrombin or serum containing thrombin and thromboplastin may be introduced into the circulation in quantities that in the test-tube would cause rapid and firm clotting and yet no harm be done. It is apparent, therefore, that a healthy animal, and probably also an individual having pathological hemorrhages, may exhibit a protective response against the effects of substances which would endanger life by the formation of intravascular clots. The nature of this defensive reaction consists, it is thought, in the formation within the organism of a compensatory amount of antithrombin to bind either the injected thrombin or to neutralize the tissue extracts introduced into the circulation. This hypothesis would explain the results which we obtained following the intravenous injections of kephalin solutions into animals. The immediate effect of intravenous injections was an increase in the coagulability of the blood. This increased coagulability was only transitory, however, and was followed soon by a return of the blood to a normal state, or in a few instances by a decreased coagulability. In hemophilic patients we could demonstrate little change in the blood after intramuscular injections of kephalin. As to the effect of intravenous injections we have no data to present, because we did not feel that the intravenous injections of tissue extracts were entirely devoid of danger.

Local Treatment. It has been my purpose in this paper to deal more particularly with the general treatment of pathological hemorrhage, but it may be worth while to say a word in regard to one or two measures which have proved to be of value in the treatment of uncontrollable hemorrhage from external wounds so frequently met with in hemorrhagic conditions.

Of the measures recommended for the control of external bleeding it would appear that the local injection of whole blood, defibrinated blood, and of serum into the tissues about the bleeding surface have all given good results. Whole blood and defibrinated blood are to be preferred because they contain cellular elements which upon disintegration furnish a coagulation-accelerating substance or

thromboplastin (also designated "zymoplastic" or "thromboplastic substance"). For these reasons tissue extracts rich in thromboplastin have long been employed.

To such an extract prepared from brain tissue reference has already been made in the paragraphs on general treatment. Kephalin can be prepared according to the method of Howell.[28] It is soluble in ether, but insoluble in alcohol, acetone, and water. In the latter it forms a milky emulsion. Unlike saline or aqueous extracts it can be sterilized without weakening its action. Howell has called attention to this difference between saline or aqueous extracts and ethereal extracts. He has shown that heating the former precipitates the protein together with the active phosphatid; whereas if the phosphatid is first extracted with ether the residue may be dissolved in water and the emulsion thus obtained is unaffected by boiling.

The various preparations of kephalin obtained may be standardized by testing their action on specimens of blood *in vitro* or by determining their coagulation-accelerating effect upon mixtures of oxalated plasma (fibrinogen) and fresh serum (thrombin). In this way we have become convinced that *in vitro* even high dilutions of kephalin will markedly accelerate the clotting of blood. The details of these tests will be recorded at a later date.

Clinical studies have shown that kephalin exerts an equally potent hemostatic action when brought into contact with wounded tissues. From our observations on hemophilia we have become assured that kephalin applied locally to the bleeding wounds of hemophiliacs brings hemorrhage to an early arrest.[2] And a number of reports[29] have appeared recently testifying to its great value also when applied to oozing wounds or hemorrhages from bone, kidney, muscle, and other tissue surfaces.

SUMMARY AND CONCLUSIONS. The clinical and experimental work of recent years has made possible a more logical classification of hemorrhagic diseases. Although it may be premature to speak of an etiological classification, more emphasis should be laid upon the experimental studies thus far carried out in the grouping of these conditions.

On this basis we may group a number of etiologically heterogeneous diseases about some defect or defects in the factors concerned in blood coagulation. Although more than one element may show an abnormality, it is permissible to designate these groups according to the essential defect present. And we may speak of a platelet group or a prothrombin group and the like, meaning that a lack of platelets or a deficiency of prothrombin is in the greatest measure responsible for the pathological hemorrhages observed.

In the study and in the grouping of hemorrhagic diseases a number of methods are now available which because of their simplicity possess great clinical value. And we believe that every instance of

obscure hemorrhage should be studied by these methods for the purpose of finding out whether the cause is attributable to an abnormality in blood coagulation. As has been pointed out, some of the tests have great practical importance in diagnosis and treatment. It may be well to emphasize that the existence of a hemophiliac condition ought to be excluded by *in vitro* tests preliminary to any operation upon a patient exhibiting the hemophiliac tendency.

Greater attention should be paid to experiment in determining the value of therapeutic measures in the constitutional treatment of hemorrhage. Observations on the clinical improvement and on the cessation of hemorrhage after treatment should be supplemented by studies upon the clotting time of the blood and the factors of coagulation before and after the institution of such therapy. In this way it will be possible to arrive at a more rational treatment of these cases.

Tested by such criteria, whole blood, we believe, is at present the most logical and most efficacious therapeutic agent for the control of bleeding in the greatest number of patients showing hemorrhagic tendencies. In the majority of instances calcium therapy has not yielded good results and the value of serum treatment has been much overemphasized.

Of the local hemostatic agents recommended, kephalin gives promise of being an important adjunct in the treatment of bleeding from external wounds. It is to be hoped, therefore, that this tissue extract will prove of real value in the control of the immoderate hemorrhages from the wounds which so frequently complicate the hemorrhagic diseases.

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COLON BACILLUS PYELITIS CONSIDERED WITH REFERENCE TO CASES IN BOY SUBJECTS.

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Laruelle and Tavel, in 1889, first found the colon bacillus in the living subject outside the intestinal tract.[1]   In 1893 Park[2] made a review of the literature on this subject and assigned to Welch[3] and Councilman credit for the name "colon infection," and to Clado and Albarran priority for classifying Bacillus coli communis as a urinary pyogenic organism (Rawls).[4]   The importance of urinary infections in children was first emphasized by Escherich in 1894, but the prevailing form was considered by him to be a cystitis.[5]   A few months later Holt[6] reported three cases which he described as those of pyelitis. Since then the literature has been steadily augmented until the subject of colon bacillus infection of the urinary tract has become one of the most common under study. Particularly, the importance of this type of infection in children is gradually receiving wider recognition.

Occurrence and Pathogenesis. Bassler[7] found colon bacilli in the urine of 9 per cent. of 191 adults having no urinary symptoms or constitutional disturbances, and therefore expressed the view that the organism may exist in the urine without active prolifera-

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[4] Loc. cit.
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tion and practically without injurious effect. The possibility that this bacillus may thus inhabit the urinary tract of a child without at some time causing serious effects will seem doubtful to many; and yet cases in children who have passed through the acute febrile stage of pyelitis and continue to show the excretion of bacteria and even pus, over a period of months, but without clinical symptoms, are extremely common.

The predominance of urinary infection in girls has long been recognized. Cnopf reports that of 40 children who had colon cystitis associated with enteritis, 8 were girls.[8] Elterich[9] saw 19 cases of urinary infection during a period of two years, in children between the ages of seven and a half months and eight years; and all of the patients were females. Of 26 cases reported by Still,[10] 23 occurred in girls. In 1911–12 cases of pyelitis and pyelocystitis comprised 5 per cent. of all the admissions at the Children's Hospital at Freiburg, and 95 per cent. of the patients in this group were females.[11] Statistics upon this phase might easily be multiplied, giving ground to the view that the infection is most frequently transmitted by direct extension upward through the lumen of the urethra, and that the other two modes of transmission (hematogenous and transparietal infection) are exceptional. On this point, however, the recent work of Eisendrath and Kahn,[12] showing the role of the lymphatics in ascending renal infection, is definitely convincing. The infection most frequently progresses upward through the lymphatic capillaries by way of the submucosa of the bladder and the peri-ureteral sheath. The close anatomical relationship of the rectum and urethra in the young female is quite probably of greater importance in this transmission of bacteria than the mere proximity of the anal and urethral orifices. Wieder found that colon bacilli injected into a rectum which had previously been traumatized could be recovered from the bladder. In this connection, moreover, the possible agency of the thread-worm in conveying bacteria from the rectum to the urethra and bladder has been remarked; while Langstein[13] has called attention to the frequency of pyelitis as a sequel of Hirschprung's disease.

Without entering further into a consideration of the etiological and pathological factors concerned, I desire especially to call attention to the clinical possibilities presented by urinary infection in the male child, and to this end offer records of three such cases.

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CASE REPORTS.

CASE I.—H. A., five years old and the youngest of three children, has a negative family history and had been free from serious illness prior to the development of the condition which is the subject of this report. He had, however, always been delicate in appearance, and for several weeks preceding this illness had appeared "pale and poisoned-looking."

Case I.   Rash recurrent during the course of pyelitis.

Early in January, 1915, this patient developed slight puffiness of the face, and simultaneously an eruption of irregularly outlined reddish macules ranging in area from 1 to 20 to 30 sq. cm., slightly elevated, and distributed over the face, entire trunk, and extremities, with the exception of the palms and soles. The more typical fresh lesions were circinate. This rash persisted without complete disappearance, the lesions fading and reappearing in successive crops, throughout a prodromal period of about three weeks, with no

accompanying symptoms other than mental irritability, pallor, and obstinate constipation. By the expiration of this period the patient had developed a septic type of temperature ranging from 99° to 103°, headache, pain in the back (especially the right lumbar region), soreness and stiffness of the legs (prohibiting standing and passive extension), and a cough suggestive of pertussis.

All of the signs and symptoms persisted without significant abatement until February 21, at which time a correct diagnosis was made possible by telephone as a result of the well-grounded refusal of the patient's attending physician to reconcile the symptom-complex with any other primary condition than intestinal toxemia, notwithstanding the fact that miliary tuberculosis, grippe, whooping-cough, typhoid fever, meningitis, otitis, and poliomyelitis had all received the consideration of those in attendance. It was thus suggested that the examination of the urine, which had been for the most part chemical, be supplemented by repeated searches for pus and bacteria, that a blood smear be examined to exclude the possibility of the presence of trichinosis, and that pending positive findings, urotropin be administered. Thereupon the urine was found to contain "pus cells" to the number of about 100 per field (low power), and a heavy cloud of bacteria. (There was no eosinophilia.)

Hexamethylenamin was administered in doses of 20 grains daily, in conjunction with acid sodium phosphate, and within three days the temperature had subsided, and the constitutional symptoms had abated. After about ten days, however, the skin eruption, which had mostly disappeared, again became marked; the urine, which had been fairly free from pus, was observed to be dark brown and turbid, and the temperature rose to 103°, persisting at this as a maximum, with remissions to 100°, during the succeeding five days.

Physical examination March 7 was practically identical with that recorded at Roosevelt Hospital March 31 (see below).

Blood: Leukocytes, 17,000; polynuclears, 56 per cent.; mononuclears, 33 per cent.; eosinophiles, 1 per cent. Agglutination test with three strains of Bacillus coli communis negative.

Urine: Very cloudy; slightly acid; specific gravity, 1014. Albumin present in a very faint trace. Microscope reveals a few hyaline casts, many pus cells closely adjacent and in clumps, and numerous bacilli. Culture of a specimen aseptically collected shows pure growth of Bacillus coli.

The hexamethylenamin and acid sodium phosphate were now discontinued, and an "A B C" mixture combining acetate, bicarbonate, and citrate of potassium was administered in dosage aggregating 60 to 80 grains daily. The temperature subsided within thirty-six hours and remained subnormal throughout a second period of improvement, during which the urine was alkaline and free from

pathological sediment except for the presence of many bacteria and about 20 pus cells per field.

An attempt at the end of ten days to replace the alkali by "amphotropin" in dosage of 15 grains daily was promptly abandoned because of the observation that within forty-eight hours the urine had again become strongly acid and contained occasional red blood cells. Moreover, before the alkali could be resumed the patient had a recurrence of acute symptoms, including the rash and a temperature of 104°; and on the night of March 26 this attack culminated in cardiac weakness and partial collapse. At the end of four days, however, following stimulation and an initial dose of vaccine prepared from the culture of March 7, sufficient improvement had taken place to warrant his removal, a distance of 200 miles, to Roosevelt Hospital.

Physical examination upon admission March 31 was negative except for the following points:

"Child is poorly developed, pale, and looks chronically ill. Lymph glands: postcervical and axillary 'shotty.' One or two bean-sized inguinal. In left lower abdomen are a number of bean-sized masses, discrete, freely movable, not tender, which seem to coalesce with the inguinal group and are palpable deeply, extending upward to the level of the umbilicus. Skin moist. On both legs are many circinate, macular lesions."

During a stay of three months in the hospital this patient was given two courses of autogenous vaccine, comprising a total of fifteen injections in dosage which was increased from 25,000,000 to 180,000,000 organisms. The vaccine apparently produced no untoward effects, but its value in this instance may be regarded as unproved because of the recurrence of temperature ranging from 101° to 104° over three separate periods of five days each before discharge of the case. On one of these occasions tenderness over the right kidney was noted coincidently with a leukocytosis of 34,000 and a polynucleosis of 92 per cent.

Relapses, indicated by a return of the fever, were invariably attended by increased acidity of the urine, even during the administration of large doses of alkali, which was given steadily either in the form of potassium citrate (40 to 50 grains daily) or in that of the "A B C" mixture supplying a combined total of acetate, bicarbonate, and citrate ranging from 135 to 270 grains daily. An acid reaction persisted on one occasion (April 29 to May 19), when the dosage of the "A B C" diuretic was as high as 270 grains. The acidity in terms of decinormal sodium hydroxide varied during this period from 24 to 0.04 c.c., averaging 6.55 c.c. Following the discontinuance of the alkali the average acidity during the next five days rose to 20.4 c.c., falling to 6.14 c.c. upon the resumption of the alkali in dosage of about 150 grains daily. For several weeks before the patient's discharge, calcium lactate was given to the

amount of 24 grains daily in conjunction with the sodium citrate, which was maintained at 30 grains daily, on the assumption that the calcium might be less depressing, less productive of fluid retention, and possibly of more favorable influence on the cutaneous eruption than the sodium and potassium salts when given exclusively. The average acidity for a typical nine days of this period was 30.4 c.c.

This boy gained $4\frac{1}{2}$ pounds during his hospital stay, and has remained in fairly good health during the two years following his return home, but at various times he has had a temperature ranging from 100° to 101°, mild outbreaks of the characteristic rash, and a slight degree of pyuria.

CASE II.—J. H. F., aged ten years, the second of three children, with negative parental history, had whooping-cough at two years and measles at four years. Pin-worms had been noted, and eneuresis had always been annoying. In general, however, his health had been good.

June 30, 1914, this boy was brought to Vanderbilt Clinic for treatment of chronic eneuresis, cough which had been recurrent over the period of a year, anemia, and loss of weight.

On physical examination he was found to be fairly well developed, but pale and listless, with a temperature of 101°. The tongue was heavily coated and the breath offensive. The tonsils showed moderate enlargement, the breathing was abnormally oral, and the cervical lymph nodes were palpably enlarged. Auscultation of the chest detected many coarse rales, most numerous at the base of the right lung. Those heard low in the right axillary region were thought to be pleuritic.

The only diagnoses offered to explain these findings were (1) pulmonary tuberculosis, and (2) bronchopneumonia accompanied by pleurisy with a small effusion in the right thorax. A von Pirquet test proved negative. Fever was not noted after July 3, and in the period up to August 19 the patient's general condition slowly improved, although the cough and physical signs referable to the right chest persisted in lessened degree for about three weeks. The weight observations were: June 30, $52\frac{1}{4}$ pounds; July 15, 53 pounds; July 23, 54 pounds; August 5, $55\frac{1}{4}$ pounds; August 19, 55 pounds. On the last date the patient passed from observation in apparently good condition and was not seen again until October 5. In the interval his health improved and the weight increased to $58\frac{1}{2}$ pounds, although cough continued annoying in the morning. When seen two weeks later, however, he was distinctly ill, having had bronchitis for several days and lost $5\frac{1}{2}$ pounds. His temperature was 101.6° and rales were again heard throughout the chest, especially at the old location in the right axilla. The von Pirquet test was repeated, but was again found negative. In the next few days the cough subsided, and a radiograph October 23 failed to reveal any intrathoracic lesions.

At this time attention was again directed to the eneuresis; and upon routine examination preparatory to treatment the urine was found to be turbid from the presence of pus which filled the entire microscopic field.

Treatment with hexamethylenamin alternating weekly with sodium citrate was now instituted; and although the patient's attendance at the clinic was irregular and he did not report from November 23 to December 23, on the latter date the urine was found to be clear and free from pus. The improvement inaugurated apparently with this treatment continued without interruption, so that by the middle of January, 1915, he weighed $58\frac{3}{4}$ pounds (6 pounds more than on his first visit), and except for a moderate tendency to eneuresis, he had no complaints. He now passed from observation for a period of over three months.

May 12 a message was received from the patient's home stating that he had been ill for a month and was thought to be dying from pernicious anemia. He was found semicomatose, but suffering visibly from orthopnea and air hunger. The face and limbs showed only slight edema, but the combined symptoms were unmistakably those of uremia, and the existence of this condition was confirmed by examination, showing the presence of albumin in the urine in amount approximating one-fourth its volume. On the same night three convulsions supervened, one lasting over a half-hour. During May 13 and 14, however, following the giving of chloral and sodium bromide by the bowel and stimulation hypodermically with caffein and digitalis, combined with measures to promote elimination, there was unexpected improvement.

Throughout the next few days repeated examinations of the urine failed to afford findings essentially different from those of May 12. Despite the constant presence of albumin in large amount, the specific gravity remained between 1008 and 1015, and the sediment uniformly failed to reveal pus cells, blood, or more than a few granular and hyaline casts. For an acute nephritis with such marked albuminuria the specific gravity was unusually low and the pathological sediment unusually scanty.

May 21, after a week without appreciable improvement, the patient was removed to Roosevelt Hospital.

Physical Examination upon Admission. "A well-nourished boy, in appearance chronically ill, showing marked pallor of the skin and mucous membrane, but no dyspnea, cyanosis, or jaundice.

Eyes and ears negative.

Axillary and inguinal lymph nodes 'shotty.'

Chest normal in contour with good respiratory excursion.

Lungs clear.

Heart: Apex impulse in fifth space 8 cm. to left of median line. Cardiac dulness corresponds. Sounds at apex regular, slightly rapid, and of good quality. First sound is followed by a soft,

blowing, systolic murmur. There is a slight pleuropericardial friction sound. At the pulmonic area a soft systolic murmur precedes the pulmonic second sound.

Extremities show very slight edema. Knee-jerks normal. No Kernig."

June 2 the patient developed slight bleeding from the gums, and on June 7 vomited a little bright red blood. Drowsiness now became very marked and the breath took on an ammonia odor. Coma ensued without recurrence of convulsions and death followed on June 8.

The hospital chart records a retinal examination June 8, showing papillary edema and areas of exudation indicative of albuminuric retinitis, a blood culture the same day with no growth, blood-pressure ranging from 135 to 140 mm., phenolphthalein tests May 25 and June 2 showing respectively 10 per cent. and 0 dye excretion, and a special urine examination May 26 showing 139 mg. of non-proteid nitrogen per 100 c.c. of blood. In spite of these features the twenty-four hours' urine excretion recorded up to two days before death only once fell below 600 c.c., and the routine tests during the last six days invariably failed to show a specific gravity above 1012, or the presence of albumin, pus, or more than an occasional hyaline cast. Tests for acetone and diacetic acid during the last three days were also negative. A blood count June 3 showed: hemoglobin, 32 per cent.; red cells, 2,995,000; leukocytes 21,400; polynuclears, 77 per cent.; lymphocytes and large mononuclears, 18 per cent.; basophile cells, 2 per cent.; myelocytes, 3 per cent.; and many microcytes. The temperature was practically afebrile.

Autopsy was not granted.

The hospital diagnosis was "chronic uremia; chronic interstitial nephritis (glomerulonephritis); simple anemia."

CASE III.—A. E., aged three and a quarter years, the first child of healthy parents, had purulent otitis media at one year of age, but thereafter was well until about twenty months old.

January, 1914, this patient had an attack of enterocolitis and developed convulsions which were followed by a period of fever not satisfactorily explained at the time, and lasting two weeks. A similar attack occurred the following March, also characterized by a convulsion, and accompanied by fever which persisted four days. At this time the urine was examined and found to contain pus.

Treatment with hexamethylenamin was given and prompt improvement ensued, but in the interval until August, 1915, there was a relapse every two or three months, with fever for a few days, and increase of the pyuria, which was never completely lacking even in the intervals between attacks. Hyaline casts were occasionally found, and on one occasion while taking the hexamethylenamin the patient had pain on micturition and slight hematuria.

In May, 1915, the administration of potassium citrate in dosage of 45 grains daily was begun and thenceforth continued at weekly intervals, alternately with the hexamethylenamin. The improvement which followed, however, was broken by relapses in June and July.

Physical examination August 8 showed the child to be slightly anemic, but in good musculature, weighing 31 pounds. The tongue was coated and the right tonsil was slightly enlarged. Cardiac examination detected slight impurity of the first sound as heard in the precordial region, but no organic murmur. The abdomen was unduly prominent. In other respects the findings were negative, except for the urinary examination. This revealed the presence of a moderate number of discrete pus cells.

The hexamethylenamin was discontinued and sodium citrate in dosage of 40 grains daily was prescribed in conjunction with culture of Bacillus Bulgaricus and syrup of the iodide of iron. This treatment was continued indefinitely, and three months after its commencement a report was received stating that the patient had had no relapse and was in better condition than at any time since the discovery of the pyelitis. A urine examination November 27, 1915, showed a very faint trace of albumin and a growth of staphylococcus (apparently due to contamination), but no pus or bacilli.

This case is of interest principally because of the existence of a temperature record kept faithfully by the boy's parents and based on observations morning and evening over a period of a year and a half. The report shows that there were seven distinct relapses of the pyelitis, each of which was productive of fever of 102° or higher, during the period of one year.

SIGNIFICANCE OF PYELITIS IN BOYS. Information derived from so small a group of similar cases is necessarily meager, especially since the chronicity of urinary infection of the type under discussion precludes the possibility of sufficiently prolonged individual observation in a given case. Certain general facts, however, seem worthy of special emphasis.

The finding of pus in a male child's urine (in the absence of a specific urethral discharge) should invariably suggest infection of the urinary tract by blood or lymph-stream absorption rather than by direct urethral contamination, which has been shown to afford a very inaccurate explanation of the occurrence of pyelitis, even in the female subject. Pyelitis in the male thus calls for the consideration of the possible existence of an intestinal focus or defect contributing to the escape of the colon bacillus from its normal habitat; and furthermore, pyelitis under these conditions should at least suggest the possibility of colon bacillus septicemia.

Of more practical value is the lesson that in cases of obscure fever in boys as well as girls, microscopic examination of the urine

should never be omitted. History of recent grip or enteritis renders the existence of pyelitis only the more probable, because of the frequency with which pyelitis has been shown to follow these diseases.

The cases reviewed demonstrate more particularly the following clinical facts:

1. Simple pyelitis when subacute, although an undoubted menace. may not prevent a child's physical progress or interfere with a fair degree of health. (Cf. Cases I and II.)

2. Nephritis of fatal outcome may, nevertheless, supervene in kidneys previously subject to pyelitis, even while the urine is clear, of low gravity and albumin content, and free from pus. (Cf. Case II.)

3. Enlarged lymph glands, a recurring skin eruption, pronounced nervous manifestations almost meningeal in type, pains in the muscles, stiffness of the joints, and cough may occupy the foreground in this condition, just as similar symptoms may predominate over the intestinal manifestations in typhoid fever. (Cf. Case I.)

4. A leukocytosis of 34,000 with a polynucleosis of 92 per cent., while calling for surgical coöperation, need not relegate colon bacillus pyelitis, in exceptional instances, outside the domain of medical treatment. (Cf. Case I.)

MODES OF TREATMENT. Three principal methods of attacking deeply seated colon bacillus infections of the urinary tract have been recommended: the administration of drugs excreted in the form of urinary antiseptics, the giving of alkali in some form, and the injection of colon bacillus vaccine.

Hexamethylenamin. Of the so-called urinary antiseptics this alone has gained extensive use in pyelitis. This drug, however, has repeatedly been shown to be without inhibitory or bactericidal action except by virtue of its liberation of formaldehyde, a chemical change occurring only in an acid medium. For this reason it is customary to administer acid sodium phosphate separately while the hexamethylenamin is given, in order to render the urine strongly acid. Burnam's test for formaldehyde[14] has been perfected, with a view of determining actually how much is liberated under dosage with various quantities of hexamethylenamin, and a number of investigators have studied the bactericidal effects of the formaldehyde thus excreted.

Levy and Strauss[15] came to the following conclusions: "Hexamethylenamin *per se* in neutral solutions in concentrations up to 1 to 10 is neither inhibitory nor bactericidal.

Formaldehyde is formed only in the bladder in all cases except

[14] Kaufmann: A Short Method of Testing for Formaldehyde after the Administration of Urotropin, Am. Jour. Obst., lxviii.

[15] A Clinical and Bacteriological Study of Hexamethylenamin as a Urinary Antiseptic, Arch. Int. Med., November, 1914.

in those in which the acidity of the urine is higher than normal. In these cases some formaldehyde is formed in the kidneys.

The strength necessary to inhibit the growth of the colon bacillus is a concentration of 1 to 5000 or greater.

Under a dose of 7 grains three times daily formaldehyde is never present in concentrations greater than 1 to 5000.

The only organism destroyed or inhibited in growth by this concentration is the typhoid bacillus.

For the destruction or inhibition of other organisms a high acidity is necessary and this high acidity in combination with formaldehyde may produce injury of kidney tissue."

Burnam,[16] L'Esperance[17] and Jenness[18] likewise studied the excretion of formaldehyde and found that not over 60 per cent. of all adults are capable of breaking down urotropin even under dosage of 30 to 100 grains; but in conjunction with their findings must be recorded the observations of Talbot and Sisson,[19] who investigated the excretion of urotropin in 44 children and infants and found that although large doses combined with the maintenance of a high degree of acidity of the urine were often necessary, nevertheless all of the children excreted the formaldehyde.

Numerous investigators, moreover, have remarked hematuria (cf. Cases I and III) under what was considered therapeutic dosage.

Before passing final judgment on this mode of treatment, however, the clinician must give due attention to such experience as that of Freeman.[20] He gave as much as 45 grains of hexamethylenamin daily to a child of one year, 35 grains to an infant of nine months, and 25 grains to one of six months, with curative effects, notwithstanding the fact that in every instance other treatment had been employed without avail.

Alkaline Therapy. It has been shown that the ingestion of colon bacilli by leukocytes is most active in an alkaline medium,[21] and this fact, coupled with recognition of the predilection of Bacillus coli for acid media gives ground to the tenet that an alkaline reaction is favorable to the subsidence of pyelitis. Accordingly, advocates of treatment based on this theory have emphasized the need of administering potassium or sodium citrate or a similar salt in dosage sufficiently large and frequent not only to produce but con-

[16] An Experimental Investigation of the Value of Hexamethylenamin and Allied Compounds, Arch. Int. Med., October, 1912, p. 324.

[17] Boston Med. and Surg. Jour., October 24, 1912.

[18] Burnam's Test for Formaldehyde in the Urine: A Study of Two Hundred Cases, Jour. Am. Med. Assn., March 1, 1913, p. 662.

[19] Some Factors Which Influence the Excretion of Formalin in the Urine of Children and Infants Taking Urotropin, Boston Med. and Surg. Jour., April 3, 1913.

[20] The Diagnosis and Treatment of Pyelitis in Infancy, Am. Jour. Dis. Child., August, 1913.

[21] Dick: British Med. Jour., 1910, ii, 1129.

stantly to maintain alkalinity of the urine. Still[22] emphasizes the importance of administering this treatment without interruption at intervals not to exceed three hours even during the time allotted to sleep. In obstinate cases he prescribes also salol. Such beverages as Vichy and lemonade are of obvious value, and the influence of the diet upon the urine reaction is by no means to be forgotten, preference being given to fruit, milk, and vegetables rather than to meat, eggs, and bread.

Many physicians who admit the possibility of ill effects from hexamethylenamin report good results gained by alternating a course of this drug not exceeding a week, with the administration of the alkali for an equivalent period.

Vaccine. Geraghty[23] reports no improvement attributable to autogenous vaccine in any one of 13 adult cases. Chapin and Pisek[24] state that the results from vaccine treatment are very good in colon bacillus infections, but that it is practically impossible by this means to cause a total disappearance of pus and bacilli. Hugh Cabot[25] has stated that vaccines produce improvement in urinary infections in more than half the cases. These few expressions are respectively typical of many others and serve sufficiently to emphasize the variance of view in this matter. The facility, however, with which the particular strain in a given case may be isolated renders the preparation of autogenous vaccine relatively simple and contributes to the justification for its use in all persistent cases. Initial doses ranging from 10,000,000 to 30,000,000 organisms are recommended, and the rapidity of increase and ultimate limitation of the dosage are to be determined by the behavior of the case. Considerable temperature reactions with constitutional disturbances such as occur after immunizing injections of typhoid vaccine are not regarded as cause for discontinuing this treatment provided large and rapidly increasing doses are avoided.

Kidney Lavage.[26] The possibility of developing a method of ureteral catheterization to such a degree as to permit the installation of antiseptic solutions into the pelvis of the kidney in cases of pyelitis in children rests with the genito-urinary specialist. In the female subject the mechanical difficulties attending such

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[22] Common Disorders and Diseases of Childhood, 1912, p. 536.

[23] The Treatment of Chronic Pyelitis, Jour. Am. Med. Assn., December 19, 1914, p. 2211. Tr. Am. Assn., Genito-urinary Surgeons, 1910, v.

[24] Diseases of Children, 1915, p. 82.

[25] Am. Jour. Urol., 1911, vii, 131.

[26] Kretschmer, H. L., and Gaarde, F. W.: Treatment of Chronic Colon Bacillus Pyelitis by Pelvic Lavage, Jour. Am. Med. Assn., June 24, 1916, p. 2052. Ayres, W.: Colon Bacillus Infection of the Kidney, New York Med. Rec., May 31, 1913, p. 968. Geraghty: Treatment of Chronic Pyelitis, Jour. Am. Med. Assn., December 19, 1914, p. 2211.

procedure are by no means so great as to discourage trial of this method in expert hands in special instances. Thus far the excellent results obtained from this form of treatment have been practically limited to selected chronic cases in adults.

General Measures. Notwithstanding the fact that there is apparently no reason why absorption and metastasis of bacteria from the intestinal tract may not continue long after the onset of renal infection, few writers emphasize the importance of systematic attack of this primary focus. Colonic irrigations and adequate catharsis are of great value, and of no less value is the maintenance of an easily digestible diet combined with the giving of cultures of Bacillus Bulgaricus or regular doses of salol.

Any of the special methods should always be supplemented by general measures to combat malnutrition and secondary anemia as in the care of tuberculosis. An outdoor life with such play as involves only light exercise does most to ensure against relapses during the period of convalescence.

SUMMARY. Urinary infection caused by the colon bacillus has been shown to be a common and important disease affecting female children. Pyelitis in boys, although far more infrequent, is, from the stand-point of the individual case, possibly even more important.

In the male subject the possibility of extension of infection through the lumen of the urethra may be excluded, and in the treatment of *all* cases the intestine is to be recognized and dealt with as the potential source of the disease.

The possibility of the occurrence of unusual and severe systemic manifestations in well-developed pyelitis should be better appreciated.

The best routine treatment for pyelitis in children is the administration of sufficient alkali to render the urine alkaline and maintain this reaction.

If hexamethylenamin is employed the formaldehyde excretion should be watched and the urine should be examined frequently, with a view of forestalling injurious effects upon the kidney parenchyma.

In all obstinate cases autogenous vaccine should receive a thorough trial.

STUDIES OF THE CEREBROSPINAL FLUID IN ACUTE ANTERIOR POLIOMYELITIS.*

WITH SPECIAL REFERENCE TO THE COLLOIDAL GOLD, POTASSIUM PERMANGANATE REDUCTION, WEIL-KAFKA HEMOLYSIN, AND SAPONIN REACTIONS.†

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The results of the examination of cerebrospinal fluids in acute anterior poliomyelitis summarized in this report are compiled from the routine examinations and special studies‡ of cerebrospinal fluids from patients admitted to the Philadelphia Hospital for Contagious Diseases¶ during the epidemic of the summer of 1916, in an effort to contribute to our knowledge of the changes occurring in the spinal fluid in this disease and the value of its examination as a practical means of diagnosis.

Careful histological studies of the spinal meninges and cords of early experimental and human poliomyelitis infections have shown that the primary reaction of the nervous system is the production of an acute meningitis characterized by hyperemia, edema, and perivascular round-cell infiltration in the pia mater, with subsequent extension into the substance of the cord and involvement of the anterior horn cells. The spinal fluid may be altered by the passage into it of cells from the perivascular and interstitial exudate in the meninges and of serum constituents derived from the hyperemic bloodvessels.

The investigations of Gay and Lucas,[1] and Lucas,[2] confined principally to a study of the cells in the spinal fluids of monkeys experimentally infected and of 11 cases in the preparalytic stage, have shown that the total cell count of the fluid is increased considerably above the normal, the majority of the cells being of the mono-

nuclear variety. Flexner and Lewis[3] in a study of the spinal fluid
from a monkey after inoculation with the virus found a consider-
able increase in the number of cells twenty-four hours after inocu-
lation, and particularly a small cell slightly larger than a lymphocyte
showing a polyform nucleus. Sophian[4] reported an increase of
globulin in the spinal fluid of cases in the early stages. In a thor-
ough study of 233 fluids from 69 cases, Peabody, Draper and
Dochez[5] found an increased cell count, with a low or normal globu-
lin content, in fluids taken during the early days of the disease
and before the onset of paralysis; at this time the polymorpho-
nuclear cells amounted to 90 per cent. of the total, although most
fluids showed almost exclusively lymphocytes and large mono-
nuclear cells. According to these investigators analogous changes
may be found in the spinal fluid of abortive cases; all fluids examined
reduced Fehling's solution. They conclude that "the examination
of the cerebrospinal fluid in acute poliomyelitis, while giving, as
far as is yet known, no specific diagnostic criteria, is of the utmost
value as an aid to diagnosis both in preparalytic and in abortive
cases." More recent reports of similar findings have been made
by Neal and Du Bois[6] and Abramson.[7]

During the recent epidemic of poliomyelitis in Philadelphia we
have examined 868 specimens of cerebrospinal fluid from cases of
epidemic poliomyelitis admitted to the Philadelphia Hospital for
Contagious Diseases and in private practice. In a smaller number
of these the histories and clinical studies were sufficiently accurate
for purposes of analysis and correlation with the results of labora-
atory examinations, and the major portion of this laboratory report
is based upon these.

1. PHYSICAL PROPERTIES OF THE SPINAL FLUID IN ACUTE
ANTERIOR POLIOMYELITIS. The majority of the spinal fluids exam-
ined by us were water-clear or showed but a faint opalescence
when viewed against a black background. Of 316 fluids from cases
early in the stage of paralysis, but 5, or from 1 to 2 per cent. of
blood-free fluids, were distinctly turbid. Of the fluids of 6 cases
which we had the opportunity of examining in the preparalytic
stage 2 showed a faint opalescence and 4 were clear. The 5 dis-
tinctly turbid fluids were from cases on the fourth, fourth, fifth,
sixth, and sixth days after the onset of paralysis, and showed total
cell counts of more than 200 cells per cubic millimeter, many of
which were polymorphonuclears.

A small fibrin coagulum was noticed in about 10 per cent. of the
spinal fluids a few hours after they had been collected and standing
in test-tubes. We have not observed xanthochromia or excessive
fibrin formation in any specimen.

Many specimens contained small amounts of blood, and while
the presence of blood may have been due in certain cases to extrav-
asation from the hyperemia vessels of the pia, we are of the opinion

that in the majority of these fluids, blood gained access by reason of the puncture of vessel with the needle, as only the first flow of fluid contained blood.

2. Cytology of the Spinal Fluid in Acute Anterior Polio-myelitis.*   The results of total cell counts with 787 fluids from cases of epidemic poliomyelitis in all stages of the disease are shown in Table I.

TABLE I.—SUMMARY OF RESULTS OF TOTAL CELL COUNTS OF SPINAL FLUIDS IN ACUTE ANTERIOR POLIOMYELITIS.

Cells per cubic millimeter of fluid.

0 to 12.	13 to 50.	51 to 100.	101 to 500.	Over 500.
178	328	156	95	30

If the upper limit of the normal number of cells per cubic milli-meter of cerebrospinal fluid is placed at 12, of these fluids 609, or 77 per cent., showed an increase of cells. In the majority of these the increase of cells was moderate, as 80 per cent. of those fluids containing an increased number of cells the counts were not above 100 cells per cubic millimeter of fluid.

The results of total cell counts in 319 fluids from patients in various stages of epidemic poliomyelitis are classified in Table II according to the day *after the onset of paralysis.* This method of classification was necessary because many cases were not diag-nosed or sent to the hospital until paralysis was present, and histories of the preparalytic stage were inaccurate. The cell counts of five cases from private practice in the preparalytic stage are included.

TABLE II.—RESULTS OF TOTAL CELL COUNTS IN VARIOUS STAGES OF POLIOMYELITIS AFTER THE ONSET OF PARALYSIS (319 FLUIDS).

Day of disease.	Total exam.	Cells per cubic millimeter.					Percentage showing increase.
		0–12.	13–50.	51–100.	101–500.	Over 500.	
Preparalytic . . .	5	..	3	2	..	..	100
1 to 3 days . . .	125	19	52	26	24	4	84
4 to 7 " . . .	99	17	51	19	9	3	82
8 to 14 " . . .	55	9	32	8	6	..	83
15 to 21 " . . .	21	8	11	1	1	..	62
22 to 28 " . . .	10	7	2	1	..	..	28
29 to 35 " . . .	4	3	1	..	..	..	25

* In making total cell counts the ordinary leukocyte mixing pipet and the Fuchs-Rosenthal chamber were employed. The diluting fluid which stained the cells and hemolyzed any erythrocytes present was prepared as follows: glacial acetic acid, 1 c.c.; distilled water, 99 c.c.; methyl violet, crystals, 0.1 gm. This fluid was filtered before use. *Counts were made as soon as possible after spinal puncture and only of those fluids showing no macroscopic evidences of blood.* The diluting fluid was drawn into the pipet to the mark 1, the spinal fluid to 11, and the contents mixed by shaking for one minute. After loading the chamber and allowing the cells to settle for five to ten minutes all cells in the ruled-off space were counted and the number multiplied by 11 and divided by 32, which gave the total number of cells per cubic millimeter of fluid.

As shown in Table II an increase of cells was noted in all of the cases examined in the preparalytic stage, and this increase of cells was found in about 95 per cent. of cases to persist for at least three weeks after the onset of paralysis, when the total number of cells gradually approached normal numbers.

The results of differential cell counts with 87 fluids from patients in various stages of the disease after the onset of paralysis are shown in Table III.

TABLE III.—RESULTS OF DIFFERENTIAL CELL COUNTS OF SPINAL FLUIDS IN ACUTE ANTERIOR POLIOMYELITIS AFTER THE ONSET OF PARALYSIS (87 FLUIDS).

Variety of cell.	Under 25 per cent. Cases.	Between 25 to 50 per cent. Cases.	Between 50 to 75 per cent. Cases.	Between 75 to 100 per cent. Cases.
Small lymphocyte .	3	3	39	42
Large mononuclears .	85	2		
Polymorphonuclears .	77	7	1	2
Endothelial . . .	all under 10 per cent.			

As shown in Table III the small lymphocyte variety of cell predominated in the majority of fluids. In over 96 per cent. of these fluids this cell constituted 25 per cent. or more of the cells present.

Cells of the type of large mononuclear leukocytes, while occasionally found, were seldom present in large numbers.

Polymorphonuclear leukocytes predominated in less than 1 per cent. of the fluids examined (3 cases) and in over 88 per cent. constituted less than 25 per cent. of the cells present.

As previously stated the majority of these fluids were from patients in whom paralysis had occurred, whereas the predominance of polymorphonuclear cells is more likely in the preparalytic stage of the disease.

3. PROTEIN CONTENT OF THE SPINAL FLUID IN ACUTE ANTERIOR POLIOMYELITIS. The routine test for the globulin-albumin content of these spinal fluids was the butyric acid test of Noguchi. Of 868 fluids from patients in various stages of the disease this technic yielded positive reactions with 32 per cent. (Table IV). A comparative study of several similar qualitative methods have shown wide variations in the delicacy of different methods as shown in Table IV.

TABLE IV.—SUMMARY OF RESULTS OF PROTEIN TESTS WITH DIFFERENT METHODS (868 FLUIDS).

Method.	Total exam.	Results. +	−	Percentage positive.
Nonne-Apelt . . .	79	11	68	14
Noguchi	868	280	588	32
Pandy	79	24	55	30
Gordon	79	30	49	37
Kaplan	79	33	46	42

The oldest of these clinical laboratory methods for globulin-albumin in spinal fluid (Nonne-Apelt)* proved the least delicate, and the method of Kaplan, the most delicate. Gordon's method[8] proved quite simple and delicate, while our results with the Pandy test were closely parallel with those of Noguchi's test. The main objections to the latter test and that of Kaplan is the employment of the ill-smelling dilution of butyric acid.

The results of globulin-albumin tests with spinal fluids from patients in various stages of poliomyelitis after the onset of paralysis and employing Noguchi's method is shown in Table V.

TABLE V.—RESULTS OF PROTEIN TESTS (NOGUCHI METHOD) IN
VARIOUS STAGES OF ACUTE ANTERIOR POLIOMYELITIS
(270 FLUIDS).

Day of disease.	Total exam.	Results. +	Results. −	Percentage positive.
Preparalytic . . .	6	1	5	16
1 to 3 days . .	113	33	80	29
4 to 7 " . .	72	30	42	41
8 to 14 " . .	43	23	20	53
15 to 21 " . .	18	10	8	55
22 to 28 " . .	11	3	8	27
29 to 35 " . .	7	1	6	14

Of the fluids of 6 cases examined in the preparalytic stage but 1 yielded a positive reaction; the percentage of positive reactions then became gradually higher to the third week after the onset of paralysis, when a rapid decrease in positive reactions became

* *Method of Nonne-Apelt.*—This test was conducted by mixing in a small test-tube 1 c.c. of spinal fluid and 1 c.c. of a saturated solution of ammonium sulphate in water; after standing three minutes this tube was compared with a second tube containing cerebrospinal fluid only and an increase of protein was indicated by opalescence, turbidity, and visible precipitation.

Method of Noguchi.—This test was conducted by mixing in a small test-tube 0.2 c.c. of spinal fluid and 1 c.c. of a 10 per cent. solution of butyric acid in physiological salt solution followed by heating to the boiling-point; 0.2 c.c. of normal sodium hydrate was added followed by heating to boiling for a few seconds. Positive reactions were read when marked opalescence or definite floccule formation occurred after standing for an hour. Faint opalescence was regarded as negative.

Method of Pandy.—This test was conducted by mixing in a small test-tube 1 c.c. of a saturated aqueous solution of carbolic acid and one drop spinal fluid. The immediate formation of a definite cloud was regarded as a positive reaction.

Method of Gordon.[8]—This test was conducted by placing 1 c.c. of spinal fluid in a small test-tube and adding 0.1 c.c. of 1 per cent. solution of bichloride of mercury in distilled water. The development of a cloud or precipitate after standing an hour was regarded as a positive reaction.

Method of Kaplan.—This test was conducted with 0.1, 0.2, 0.3 and 0.4 c.c. of spinal fluid, but the results expressed in Table IV are based upon the reactions observed with 0.2 c.c. of fluid. This amount of fluid was placed in a small test-tube and 0.3 c.c. of distilled water added, followed by heating until the mixture boiled up twice. Three drops of a 5 per cent. solution of butyric acid in physiological salt solution was added and the mixture carefully underlayed with 0.5 c.c. of a saturated aqueous solution of ammonium sulphate. The reactions were read after standing twenty minutes and regarded as positive if a definite ring was apparent; opalescence only was regarded as negative.

apparent. As previously stated, however, and as shown in Chart 1, the cells are increased in the preparalytic and early stages of the disease, the number dropping with the globulin content after the third week following the onset of paralysis.

Accordingly we have found the total cell count alone of most value in aiding the diagnosis of acute anterior poliomyelitis; during the earliest stages of the disease the globulin-albumin tests may or may not be positive, and usually are not. In tuberculosis and meningococcic meningitis, on the other hand, the globulin-albumin tests are usually positive in the early stages, due to the greater degree of involvement of the meninges.

CHART 1.—Curves of total cell and protein increase in cerebrospinal fluid of poliomyelitis.

PER CENT. SHOWING INCREASE	DAY OF DISEASE						
	PREPARALYTIC	1 - 3	4 - 7	8 - 11	15 - 21	22 - 28	29 - 35
100							
90							
80							
70							
60							
50							
40							
30							
20							

——————— = protein curve.   - - - - - - - - - - = total cell curve.
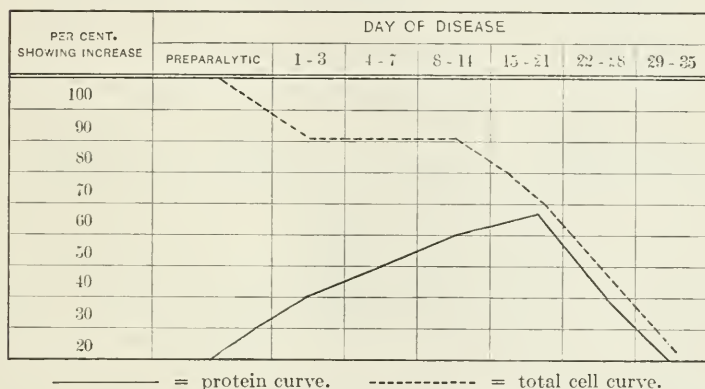
4. LANGE'S COLLOIDAL GOLD REACTION IN ACUTE ANTERIOR POLIOMYELITIS. While the exact mechanism of the precipitation of colloidal gold and the nature of the substance in cerebrospinal fluid responsible for the phenomenon are unknown it is supposed by many investigators that the precipitating substance is of a protein nature. We have examined the fluids of 38 cases drawn from two to sixteen days after the onset of paralysis with colloidal gold prepared after the method of Miller and his associates,[9] and fulfilling all the requirements of a satisfactory preparation of colloidal gold as emphasized in their paper, to determine if changes occur in poliomyelitis and whether or not these are sufficiently constant to render the test of diagnostic value. The results of these examinations are shown in Chart 2.

The fluids of 18 cases examined at intervals of two to twelve days after the onset of paralysis showed no color changes at all.

The fluids of 4 cases in the same stages of the disease showed but very slight precipitation in the first two tubes of the series as a 1,100,000,000 reaction. All of these fluids showed an increase of cells and one of them an increase of globulin (Noguchi method).

The fluids of 10 cases examined two to twelve days after the onset of paralysis yielded reactions of the "luetic zone" type with maximum precipitation in the 1 : 40 to 1 : 160 dilutions of fluid with decolorization usually terminating with "blue."

The fluids of 6 cases examined twelve to nineteen days after the onset of paralysis yielded reactions of the "meningitic zone" type characterized by maximum precipitation in dilutions of 1 : 80 to 1:320 or 1:640.   All fluids yielded negative Wassermann reactions.

CHART 2.—Summary of results of Lange's colloidal gold reaction with the cerebro-spinal fluids of 38 cases of acute anterior poliomyelitis.

TUBE NO.	COLOR	DILUTIONS									
		1: 10	1: 20	1: 40	1: 80	1: 160	1: 320	1: 640	1: 1280	1: 2560	1: 5120
5	COLORLESS										
4	LIGHT BLUE										
3	BLUE										
2	LILAC										
1	PURPLISH RED										
0	NO CHANGE										
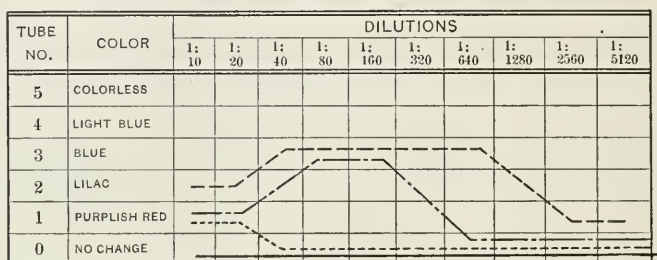
——————— = observed with the spinal fluids of 18 cases examined 2 to 12 days after the onset of paralysis.

· · · · · · · · · · = observed with the spinal fluids of 4 cases examined 2 to 12 days after the onset of paralysis.

—·—·—·— = observed with the spinal fluids of 10 cases examined 2 to 12 days after the onset of paralysis ("luetic zone" curve).

— — — — = observed with the spinal fluids of 6 cases examined 12 to 19 days after the onset of paralysis ("meningitic zone" curve).

According to these results, while 40 to 50 per cent. of spinal fluids from cases of epidemic poliomyelitis ranging from the second to the nineteenth day after the onset of paralysis tend to react in a rather constant manner, yielding reactions of the "luetic and meningitic zone" types, similar reactions occur in other forms of meningitis, and we regard the colloidal gold reaction of but helpful diagnostic value; a peculiar or definite curve of precipitation with the spinal fluid of epidemic poliomyelitis did not occur in our experience.

5. MAYERHOFER POTASSIUM PERMANGANATE REDUCTION REACTION IN ACUTE ANTERIOR POLIOMYELITIS.   Mayerhofer[10] has proposed the reduction of a decinormal solution of potassium permanganate by 1 c.c. of spinal fluid in an acid medium as an index of the amount of protein substances present and as a method of value in the diagnosis of tuberculous meningitis on the basis that while 1 c.c. of normal spinal fluid usually reduced 2 to 2.3 c.c. of $\frac{N}{10}$ potassium permanganate solution, the fluid of tuberculous meningitis may reduce 3 c.c. or more.   Hoffman and Schwartz[11] determined the index on spinal fluids of 3 cases of acute poliomyelitis with readings varying from 2.5 to 3.3 in the acute stage and showing a decline coincident with the disappearance of acute symptoms.

The technic of the test as employed by us is given below.*

We have employed this test in the study of 78 spinal fluids from cases of epidemic poliomyelitis at different stages of the disease ranging from the second to the twenty-first days after the onset of paralysis, with the following reduction indices:

0.7 to 1.1 with the fluids of 6 cases.
1.2 to 1.6 with the fluids of 17 cases.
1.7 to 2.0 with the fluids of 23 cases.
2.4 to 3.6 with the fluids of 31 cases.
6.1 with the fluid of 1 case.

According to Mayerhofer the reduction index may be regarded as increased if over 2.3; the fluids of 32 cases yielded indices over 2.4, indicating that 41 per cent. of the spinal fluids from cases of acute epidemic poliomyelitis in the first three weeks of the infection contain an increased protein content. The determination of the reduction index may be of some practical value in aiding the diagnosis of acute poliomyelitis, as indices of over 2.3 indicate the presence of increased protein due to meningitis.

6. REDUCTION OF FEHLING'S SOLUTION BY SPINAL FLUID IN ACUTE ANTERIOR POLIOMYELITIS. A qualitative Fehling's test† for the presence of dextrose was conducted with 779 spinal fluids from cases of epidemic poliomyelitis in various stages of the disease. Every fluid reduced a portion of the copper solution, but in varying amounts; with 86 fluids the amount of fluid required to effect partial reduction was so large as to indicate that the amount of dextrose was diminished below the normal, but our results in general are in accord with those of previous investigators, indicating that insofar as the qualitative test is concerned there is no constant alteration in the amount of dextrose in the spinal fluid' of epidemic poliomyelitis.

7. THE WEIL-KAFKA HEMOLYSIN REACTION IN ACUTE ANTERIOR POLIOMYELITIS. Normally the blood of over 90 per cent. of persons contains natural antisheep hemolysin, but the cerebrospinal fluid is free of this substance. In meningitis, according to Weil-

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* *Technic of the Mayerhofer Reduction Test.*—Place in a beaker 50 c.c. distilled water, 10 c.c. of diluted sulphuric acid (1 part concentrated sulphuric acid and 3 parts distilled water) and 10 c.c. of a decinormal solution of potassium permanganate; boil slowly for ten minutes and determine the amount of decinormal oxalic acid solution required to reduce the potassium permanganate solution until water clear. In a second beaker (thoroughly cleansed) place 1 c.c. of spinal fluid, 50 c.c. distilled water and 10 c.c. of diluted sulphuric acid.   Bring to boiling-point, add 10 c.c. decinormal potassium permanganate solution and boil slowly for ten minutes.   Turn off the burner and add slowly the amount of decinormal oxalic acid determined in the previous titration.   The contents of the beaker turn brown and gradually become water clear.   With a burette add decinormal potassium permanganate until the first appearance of a clear rose color.   The amount of $\frac{N}{10}$ permanganate solution required represents the "reduction index" of the spinal fluid.

† *Technic.*—0.5 c.c. each of Fehling's alkaline and copper solutions were diluted with 9 parts of water and 1 c.c. brought to boiling-point in a small test-tube; 1 c.c. of spinal fluid was added followed by brief boiling and the occurrence and degree of reduction noted after standing several minutes.

Kafka,[12] the hyperemia and increased permeability of the vessels and exudative processes results in the passage of this hemolysin into the cerebrospinal fluid. Likewise, hemolytic complement is not found in appreciable amounts in normal cerebrospinal fluid, whereas in acute meningitis this substance may be found. Tests of the spinal fluid for natural antisheep hemolysin and complement have been advocated in the diagnosis of meningitis, and particularly in those types caused by Treponema pallidum.

We have employed this test, with certain modifications,* in the study of a number of spinal fluids from normal persons, and cases of anterior poliomyelitis in various stages of the disease for the hemolysin alone and for the hemolysin and hemolytic complement. The results of these tests are summarized in Table VI.

TABLE VI.—SUMMARY OF RESULTS WITH THE WEIL-KAFKA HEMO-
LYSIN REACTION IN EPIDEMIC POLIOMYELITIS.

Reaction.	Poliomyelitis fluids.			Control fluids.			Per cent. positive in poliomyelitis.
	Total.	+	−	Total	+	−	
For antisheep hemolysin alone .	65	43	22	11	0	11	66
For the hemolysin and complement	43	13	30	4	0	4	30

The spinal fluids of 65 cases examined for antisheep hemolysin alone showed the presence of this substance in 43, or 66 per cent., whereas the fluids of 11 control persons were negative. The majority of the fluids containing the hemolysin were from cases of poliomyelitis in the acute stages of the infection.

* 1. Technic for ascertaining the presence of complement and antisheep hemolysin in spinal fluid:

In tube No. 1, 5 c.c. of fresh spinal fluid, free from all traces of blood, were mixed with 1 c.c. of a 2.5 per cent. solution of sheep corpuscles (prepared with physiological salt solution).

In tube No. 2 the spinal fluid was replaced by 5 c.c. of physiological salt solution. This tube served as a control.

The tubes were incubated at 37.5° C. for two hours and centrifugated for a few minutes and the reading of the occurrence and the degree of hemolysis immediately taken. Hemolysis in tube No. 1 indicated the presence of the complement and antisheep hemolysin.

2. Technic for ascertaining the presence of natural antisheep hemolysin alone:

Five cubic centimeter of spinal fluid free from blood and bacterial contamination and 1 c.c. of a 2.5 per cent. sheep corpuscle solution were mixed in a test-tube. A control in which the spinal fluid was replaced by physiological saline solution was also included. The tubes were incubated at 37.5° C. for one hour. They were then centrifuged and the entire supernatant fluid carefully pipetted off. To the sediment of corpuscles 1 c.c. of hemolysin-free guinea-pig complement diluted 1 to 20 with physiological salt solution was added. The tubes were well shaken, reincubated at 37.5° C. for one hour, centrifuged, and the reading of the occurrence and degree of hemolysis taken at once. The occurrence of hemolysis indicated the presence of natural antisheep hemolysin which sensitized the sheep cells followed by hemolysis after the addition of complement. The natural antisheep hemolysin in guinea-pig complement was removed by adding 0.2 c.c. of packed washed sheep corpuscles to 5 c.c. of clear undiluted complement serum. This mixture was kept in a tumbler of cracked ice for one hour, centrifuged, and the clear complement serum used for the dilution.

The spinal fluids of 43 cases examined for hemolytic complement and the hemolysin showed the presence of these substances in 13, or 30 per cent., of fluids from cases in the acute stage of poliomyelitis. The fluids of 4 control cases were found free of both complement and the hemolysin.

The results indicate that in acute anterior poliomyelitis there is present an increased permeability of the vessels with the passage into the cerebrospinal fluid from the blood of both natural anti-sheep hemolysin and complement and particularly the former; a test for these substances may therefore prove of aid in the diagnosis of this infection.

8. HAUPTMANN'S SAPONIN REACTION IN ACUTE ANTERIOR POLIOMYELITIS. Solutions of saponin are capable of hemolyzing the erythrocytes of various animals. Hauptmann[13] has found that the cerebrospinal fluid from persons suffering with various diseases of the central nervous system may contain a substance which inhibits this hemolysis. The inhibiting substance is supposed to be cholesterin and the presence of amounts in the spinal fluid sufficient to inhibit saponin hemolysis is regarded as being due to the presence of degenerating lesions with the liberation of cholesterin from the nervous tissues.

We have tested the inhibiting properties of the spinal fluids*

Technic of Hauptmann's Saponin Reaction.—We have modified Hauptmann's original technic and conducted our tests as follows: Nine cubic centimeters of human blood were obtained by venous puncture and mixed with 1 c.c. of a 10 per cent. solution of sodium citrate in physiological salt solution. The blood was then centrifuged and the supernatant fluid withdrawn. The cells were washed three times in physiological salt solution and a 7.5 per cent. suspension in physiological salt solution prepared. The stock solution of saponin was prepared by dissolving 0.5 gram of saponin (Kahlbaum Com.) in 10 c.c. of sterile distilled water. (Solution occurs readily at 37.5° C.). A 1 to 10,000 solution in physiological salt solution was made for each titration from this stock solution. (The stock solution keeps well for one month, after this time the solvent property is greatly delayed.) The titration for dose of saponin was conducted as follows: Into seven test-tubes were placed 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7 c.c. of the saponin test solution, 0.8 c.c. of physiological salt solution, and 0.5 c.c. of the 7.5 per cent. blood suspension, mixed and incubated at 37.5° C. for one hour. The next dilution of saponin stronger than the one producing complete hemolysis was chosen for the test. The test was then conducted as follows:

Tube 1: 0.8 c.c. clear spinal fluid + determined amount of NaCl + 0.5 c.c. 7.5 per cent. cells.

Tube 2: 0.2 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 3: 0.4 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 4: 0.6 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 5: 0.8 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 6: 0.8 c.c. NaCl solution + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

All tubes were incubated for two hours at 37.5° C. when the reading of the degree of hemolysis was taken, centrifugation being resorted to if necessary.

Tubes No. 1 and 6, being controls, show complete hemolysis; the presence of substances in the spinal fluid inhibiting hemolysis is indicated in the remaining tubes of the series, the degree of inhibition increasing with the larger amounts of spinal fluids.

from 30 cases of acute anterior poliomyelitis during the acute stages of the disease and the fluids of 5 control persons, with negative results in all. Amounts of spinal fluid from the control and poliomyelitis cases ranging from 0.2 to 0.8 c.c. did not produce any appreciable inhibition of hemolysis.

DISCUSSION. The results of these routine examinations and special studies of the spinal fluids from cases of acute poliomyelitis in the recent Philadelphia epidemic have essentially confirmed the findings of Peabody, Draper, Dochez, and other investigators. The greatly desired diagnostic laboratory test for acute anterior poliomyelitis, and particularly in the early stages and for those cases apt to escape clinical detection, has not yet been discovered. None of the physical, chemical, or cytological changes found in the spinal fluid are absolutely confined to acute poliomyelitis or characteristic of this disease; while specific antibodies in the serum have been demonstrated by neutralization of the virus *in vitro* as determined by intracerebral injection into monkeys, this is not a practical diagnostic method and attempts to demonstrate complement-fixing antibodies in the serum and spinal fluid have yielded mostly negative results in the experiments of Gay and Lucas[14] and Kolmer and Freese.[15]   Likewise, the microparasite of poliomyelitis discovered by Flexner and Noguchi[16] apparently cannot be cultivated from the cerebrospinal fluid and blood during life, but only from the nervous tissues after death by special methods and under exceptional difficulties, and bacteriological examinations therefor are not available for diagnostic purposes. The easily cultivated streptococci and diplococci found in the brain, cord, and spinal fluid of poliomyelitis, and recently given renewed prominence by the reports of Mathers,[17] Rosenow, Towne and Wheeler,[18] and Nuzum and Herzog[19] do not, in our opinion, possess any diagnostic value; the studies of Kolmer, Brown and Freese[20] with these bacteria are in accord with those investigators who have disregarded these microörganisms as the etiological agent of the disease; we regard these cocci as bearing a relation to poliomyelitis similar to streptococci in scarlet fever. Cultures of the cerebrospinal fluid in acute poliomyelitis during life are sterile in many cases and the presence of an easily cultivated bacterium is always suggestive of contamination. Streptococci are to be found in the tissues of the nervous system and internal organs but only exceptionally in the cerebrospinal fluid during life.

The extent of the changes in the spinal fluid appear to be dependent upon the degree of hyperemia and cellular and serous exudation in the pia mater. As the meningitis produced by the microparasite of poliomyelitis is of an interstitial character rather than a surface infection the alterations of the cerebrospinal fluid from the normal in acute poliomyelitis are not usually as extreme

as found in such infections as those produced by the meningococcus and pneumococcus. For this reason the examination of cerebrospinal fluid must be thorough and employ delicate methods for the detection of abnormal changes. Similar changes in the spinal fluid may occur in tuberculous meningitis, and requires very careful and painstaking search for the tubercle bacillus in the differential diagnosis between the sporadic and atypical case of acute poliomyelitis and tuberculous meningitis. Usually no difficulty is encountered in differentiating from such forms of meningitis as those produced by the meningococcus, pneumococcus, and influenza bacillus on the basis of the high total cell counts, presence of polymorphonuclear leukocytes, large amounts of protein, and the specific microörganism in the cerebrospinal fluid in these infections. The spinal fluid in "serous meningitis," or acute meningeal congestion, may resemble the fluid in acute poliomyelitis insofar that the fluid in both conditions may be clear and under pressure; but the absence of protein increase and an increase of cells in the former usually serve in differentiating between the two conditions.

In acute poliomyelitis a total increase of the cells mostly of the small lymphocyte variety, in a clear or occasionally opalescent spinal fluid under increased pressure, appears to be the earliest and most constant change, while an increase of protein with slight or no alteration in the dextrose content are additional data of value, as are probably also the presence of natural antisheep hemolysin and a substance partially precipitating colloidal gold in dilutions of fluid ranging from 1 : 40 to 1 : 320.

SUMMARY. In the recent epidemic of poliomyelitis in Philadelphia the examination of cerebrospinal fluids yielded the following results:

1. The majority of the fluids were water clear or but faintly opalescent when viewed against a black background; but 1 or 2 per cent. of blood-free fluids presented distinct turbidity. Xanthochromia and excessive fibrin formation were not found; about 10 per cent. of the fluids presented a small fibrin coagulum after standing several hours.

2. Seventy-seven per cent. of the fluids from all stages showed an increase of total cells; in 80 per cent. of these the counts were not above 100 cells per cubic millimeter of fluid. An increase of the total cells was found in the preparalytic stage, and this increase was present in 95 per cent. of cases for at least three weeks after the onset of paralysis, after which the number of cells gradually decreased.

3. In over 96 per cent. of fluids from cases after the onset of paralysis the small lymphocyte variety of cells predominated. Polymorphonuclear cells predominated in less than 1 per cent. of fluids, and in over 88 per cent. constituted less than 25 per cent. of the cells present.

4. An increase of protein was found in 32 to 42 per cent. of fluids, and different tests for protein yielded varying results. With the Noguchi test the fluid of 1 of 6 cases in the preparalytic stage yielded a positive reaction; the percentage of positive reactions then became gradually higher to the third week after the onset of paralysis (55 per cent. positive), when a rapid decrease in protein became apparent.

5. During the acute stages of poliomyelitis the fluids of 40 to 50 per cent. of cases yielded a colloidal gold reaction of the luetic and meningitic zone types. All yielded negative Wassermann reactions. The balance of these fluids produced no precipitation at all, or but slight changes in the 1 : 10 and 1 : 20 dilutions.

6. The potassium permanganate reduction test yielded positive reactions of indices over 2.3, with the spinal fluids of 41 per cent. of cases examined from the second to twenty-first days after the onset of paralysis; a high reduction index indicates an increase of protein in the fluid, and may aid, therefore, in the diagnosis of acute poliomyelitis.

7. Every fluid was found to contain sufficient dextrose to reduce Fehling's solution in some degree; partial reduction of the amount of dextrose was suspected with a number of fluids on the basis of a qualitative test.

8. Increased permeability of the meninges was indicated by the presence of natural antisheep hemolysin in the fluids of 66 per cent. of cases in the acute stages and both the hemolysin and a hemolytic complement in 30 per cent. Both of these substances were absent in the fluids of control persons.

9. Substances inhibiting saponin hemolysis were not found in the fluids of cases two to twenty-one days after the onset of paralysis.

10. A definite and absolute diagnostic criterion or laboratory test with the cerebrospinal fluid in acute anterior poliomyelitis has not been discovered. A clear or slightly opalescent fluid flowing under increased pressure, sterile as examined by smear and culture when collected aseptically, poor in fibrin, reducing Fehling's solution and containing an increased number of cells chiefly of the mononuclear variety, are the most constant findings. An increase of protein and a high potassium permanganate reduction index strengthen the diagnosis, while a colloidal gold reaction of the luetic and meningitic zone types and the presence of natural antisheep hemolysin are helpful diagnostic data.

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POST–TRANSFUSION REACTIONS: A REVIEW OF 280 TRANSFUSIONS PERFORMED IN THE WARDS OF PRESBYTERIAN HOSPITAL, NEW YORK CITY.

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Transfusions can now be performed with such ease and safety that their use has become very popular in a great variety of clinical conditions.   In fact, the treatment is probably resorted to in many cases in which it does no good, and perhaps does harm to the patient. It is therefore worth while to determine the conditions in which

transfusions are of benefit, and to eliminate their use from conditions in which they are useless, lest they fall into disrepute by unintelligent use, only to be revived when their real value can be more definitely determined. The febrile reaction which so frequently follows transfusion is an unpleasant phenomenon, the nature of which is as yet very poorly understood, and which is sometimes so severe as to be alarming. The purpose of this review is to discover in which conditions transfusion is a proper therapeutic measure, what the real cause of the post-transfusion reaction is, and what factors in its production can be eliminated.

We have reviewed 280 transfusions performed on 99 different patients, 57 of whom were males, 42 females; 35 were suffering from surgical conditions, 64 from medical conditions. In the surgical cases transfusion was performed in three general types of cases: (1) just before or during operation to prevent shock or counteract excessive hemorrhage, (2) for postoperative hemorrhage, (3) as a last resort in desperately sick patients after operation. Among the medical cases, 40 were suffering from pernicious anemia. These cases comprise the major part of our series, and 164 transfusions, 58 per cent. of the whole series, were performed on them. The other medical cases are in four classes, namely, (1) other blood diseases, such as leukemia, Hodgkin's disease and splenic anemia; (2) secondary anemias, including cases of acute hemorrhage from various causes; (3) cases of bacteriemia.

The question of the therapeutic value of transfusion, and what the indications are for its use, involves the careful study of temporary and permanent effects in the conditions in which it is used. For this there is not space in this review. The cases in which it was used in our series were very largely cases suffering from incurable disease, the treatment being used merely as a palliative measure. This is shown by the final outcome of the cases:

Cured . . . . 10 per cent.
Improved 36   "
Unimproved 6   "
Died 48   "

This, however, does not detract from the value of transfusion, for many cases of incurable disease, such as pernicious anemia, have been given months of fairly good health, and in many cases spontaneous remissions have been definitely hastened. The cured cases in our series were, with one exception, clean operative cases transfused just before, during, or after operation. The other cured case was one of typhoid fever with intestinal hemorrhage. The cases discharged "improved" include many cases of pernicious anemia and cases of hematemesis or other forms of acute hemorrhage in which transfusion seems to be of distinct advantage. The unimproved cases and those which died include incurable primary

blood disease and cases of sepsis and bacteriemia. These latter, whether surgical cases with undiscovered foci of suppuration, or medical cases of bacteriemia, benefited least by transfusion, not a single case having recovered. The other condition in our series which seems distinctly not to have been helped even temporarily is acute leukemia.

METHODS OF TRANSFUSION. The methods of transfusion used in this series were as follows:

Sodium citrate method	196 transfusions,	70.0 per cent.
Syringe cannula method (Lindemann) .	73 "	26.4 "
Defibrination method	5 "	1.8 "
Washed blood cells	3 "	1.0 "
Arteriovenous suture	2 "	0.8 "
Hirudin method	1 "	0.4 "

In the sodium citrate method, perfected by Lewisohn,[1] the blood was taken through a large needle from a vein at the donor's elbow into a flask containing sodium citrate solution. In no case was it necessary to cut down on the donor's vein. 5, 8 or 10 per cent. sodium citrate solution was used, made up from chemically pure sodium citrate crystals dissolved in freshly distilled water and sterilized in an autoclave. The final dilution of sodium citrate averaged 0.5 per cent. Although blood can usually be kept from clotting by a 0.2 per cent. solution, it has occasionally clotted with that dilution during administration, and since toxic symptoms were not observed in our series from as much as 5 gms. of the drug, which is equivalent to 0.5 per cent. in 1000 c.c. of blood, the latter dilution has been considered better. After collecting the blood it is strained through sterile gauze into a second flask to remove any small clots, and is administered by drawing it through glass tubing jointed with short rubber tubes, through a 3-way stop-cock into a glass syringe, and is thence injected through the stop-cock and a medium-sized needle into the recipient's vein. This syringe method of administration is used because it is frequently difficult to enter and stay in the recipient's vein with a needle large enough to let the blood flow by gravity, and it is quicker and neater, and preserves the recipient's vein better, to avoid cutting down on the vein by using the small needle. All the apparatus is sterilized in water distilled the day it is used, except the flasks and needles, which are dry sterilized. The apparatus is flushed out with citrate solution before the blood enters it, in order to prevent slight hemolysis from the water in the tubing. By this method a complete transfusion of 500 c.c. of blood can be performed by one person in about thirty minutes. It is the method which is used as a routine at the Presbyterian Hospital at the present time.

In 3 cases it was impossible to secure a donor belonging to the same blood group as the patient. A donor was therefore secured from a blood group whose cells would not be agglutinated by the

patient's serum, but whose serum would agglutinate the patient's blood cells. The blood was taken in citrate solution, centrifuged, the serum removed, and the cells washed once and suspended in an equal volume of normal saline prepared from freshly distilled water. The cell suspension was then administered to the patient in the usual way, and no untoward effect was noted in any case. Minot[2] states that no untoward symptoms occur in transfusions in which donor and recipient belong to different groups so long as the donor's cells will not be agglutinated by the recipient's serum, even though the donor's serum will agglutinate the recipient's cells. The apparent cause is the dilution of the donor's serum by that of the recipient. This was not done in any cases in our series.

The transfusions performed by means of hirudin to prevent plotting and by arteriovenous suture are included as examples of methods not now in common use.

BLOOD GROUPING. The grouping of donor's with recipient's blood to assure the absence of agglutinins and hemolysins in one blood for the other was carried out in almost every case. In 5 cases in the early days of the syringe cannula method there is no record that it was done. In one other case, No. 7, there is a statement that it was not done. In this case, one of prolonged uterine hemorrhage, 300 c.c. of blood was taken from each of two daughters by the syringe cannula method. Immediately afterward the patient complained of air hunger and pain and oppression in the chest, which was unrelieved by medication, and eight hours later she suddenly went into collapse and died. The case is considered one in which the blood of the recipient was incompatible with that of one or both donors, although no examination of the blood or urine of the recipient was made after the transfusion.

In all except the above 6 cases, donor's and recipient's blood were either tested directly against each other or were grouped according to the method of Epstein and Ottenberg.[3] Table I shows the agglutination and hemolysis reactions which are the basis of this grouping, the plus sign standing for hemolysis and agglutination of the cells by the corresponding serum.

TABLE I.

	Group.		I.	II.	III.	IV.
Cells	I	. . . .	0	0	0	0
	II	. . . .	+	0	+	0
	III	. . . .	+	+	0	0
	IV	. . . .	+	+	+	0

Group I may be called the strongest group, its cells not being agglutinated or hemolyzed by the serum of any other group, and its serum containing agglutinins and hemolysins for the cells of all the other groups. Group IV, on the other hand, is the weakest group, its cells being agglutinated and hemolyzed by the serum of

all the other groups, and its serum not containing agglutinins or hemolysins for any human blood.

The technic now followed in our laboratory by Miss Miriam Olmstead for the grouping of blood is that devised by Epstein · and Ottenberg,[4] and is as follows: Samples of serum and cells of known group are kept ready for use. Two specimens of blood are taken from the person to be grouped, one in a dry test-tube and one in normal saline. The former is allowed to clot and is centrifuged to separate the serum. The blood taken in saline is centrifuged, the saline pipetted off, the cells washed and a 5 per cent. suspension in saline prepared. A drop of the cell suspension is mixed in a capillary pipet with a drop of the serum from known groups and the pipet sealed. The same thing is done with a drop of the unknown serum with known cells. The tubes are then incubated at $37°$ C. for twenty minutes, at which time they can usually be safely read. Agglutination, if present, can be detected macroscopically, the cells gathering into long strings. Hemolysis is sometimes also evident, but as agglutination is always present in incompatible bloods, whether or not there is hemolysis, the latter need not be ascertained. The pipets are then left at room temperature for two hours before the final reading is made, and in case two bloods are being matched directly and no agglutination is evident at the end of two hours, a final reading is not made until the following day.

Specimens of blood belonging to Group III are occasionally met with, Miss Olmstead tells us, whose serum has no agglutinins for Group II. The final test for these specimens, to distinguish them from Group IV, which also has no agglutinins for Group II, must be their ability to agglutinate the cells of Group IV and the inability of the serum of Group III to agglutinate their cells. As Group IV blood is usually not available, the latter point must usually be the deciding one.

It is really necessary, as Moss[5] has shown, to use only the cells of Groups II and III against the serum of the blood to be grouped, or the serum of Groups II and III against the cells of the blood to be grouped, as the cells or serum from each of the four groups will act differently toward the serum or cells of these two groups. As serum can be preserved much better than cells, the serums of Groups II and III are the most valuable specimens to have on hand. For purposes of control, however, it is wise to use blood from all three of the common groups if they are available.

A more rapid method of grouping which we use in emergency cases, and which has proved just as reliable as that given above, is as follows: The cells and serum are prepared as described above. A drop of cell suspension and serum for each test are then mixed together on one end of a glass slide, and are let stand at room temperature for five minutes. A small drop of the mixture is then

diluted with a drop of saline at the other end of the slide, and a cover-slip applied. Any agglutination is evident at once microscopically, the cells gathering together in bunches of irregular shape. The appearance is distinctly different from rouleaux formation where the cells are in chains and overlap each other regularly. Ten minutes later the agglutination is evident macroscopically in the original mixture at the other end of the slide.

Before the introduction of the classification into blood groups, donor and recipient were grouped directly in every case, but for the last two years, which covers the period of practically all the transfusions by the citrate method in this series, most of the cases have been grouped from stock specimens of known blood, and transfused from a donor whose group had been previously determined, without testing donor's and recipient's blood directly. In this way emergency transfusions have been performed on very short notice, and in no case has there been any evidence of incompatibility. In several cases blood for grouping has been taken from the donor at the time of transfusion, and donor and recipient tested directly to check up results. In no case has any incompatibility been found. Nor have the post-transfusion reactions been any more numerous during the period of the citrate transfusions, as will be shown later in Table IV. It must be said, however, that unless a reliable laboratory is at hand to carry out such a system of grouping, the direct test of the donor's blood against the recipient's is the only way to be sure of their compatibility.

Of the 67 patients in this series whose blood group was determined, the groups were represented as follows:

Group   I   .   .   .   .   31 cases, or 46 per cent.
Group II   .   .   .   .   26 cases, or 39   "
Group III   .   .   .   .   9 cases, or 13   "
Group IV   .   .   .   .   1 case, or 2   "

Groups I and II are therefore much the commonest groups.

POST-TRANSFUSION REACTIONS. The post-transfusion reaction is an occurrence which has been met with by all who have used the treatment, no matter what method of transfusion is employed. The typical reaction consists of a chill, coming on about one-half hour after the transfusion, a sharp rise of temperature, gradually subsiding to normal in three to eight hours, sometimes nausea, vomiting, pains in various parts of the body, and skin eruptions, especially urticaria and localized areas of edema. There is great variation in the degree of reaction, from a slight rise of temperature with no other symptoms, to a rise of temperature to 105° with all the other symptoms mentioned above.

In classifying our transfusions according to the degree of reaction, the rise of temperature alone has been considered. So many patients have a normal rectal temperature of 99° F. that unless

there was a rise to 100° or over the patient was classified as having no reaction. Table II shows the percentage of reactions of various degrees:

TABLE II.

Degree of reaction.	Highest temp. Fahr.	Number of transfusions.	Percentage of transfusions.
0	99.8°	102	36.4
1	100° to 101.8°	60	21.4
2	102° to 103.8°	76	27.2
3	104°+	42	15.0

It will be seen that 36.4 per cent. of the transfusions were not followed by any reaction, 63.6 per cent. were followed by some degree of reaction. These figures are therefore the control figures for the examination of the factors which may cause the reaction. These factors will now be considered.

I. *The Relation of the Recipient's General Condition to the Reaction.* Table III shows the relative number of reactions among recipients who were in good, fair, and poor condition at the time of transfusion:

TABLE III.

Condition.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Good	167	134	74
Fair	68	35	51
Poor	45	19	42

This factor is, of course, a negative rather than a positive one, for the good condition of the patient cannot be said to be a cause for the reaction. Poor condition is rather a cause for the absence of it. Nevertheless it is evident that the reaction is dependent to a considerable degree upon the ability of the body to respond to the introduction of a foreign substance.

II. *The Relation of the Method of Administration to the Reaction.* Table IV shows the comparative number of reactions following transfusions by the citrate and syringe cannula methods. The number of transfusions by the other methods in our series is too small for comparison.

TABLE IV.

Method.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Citrate	196	127	64.8
Syringe cannula	73	47	64.4

The reaction following one of the transfusions by the syringe cannula method was undoubtedly a so-called "water reaction," the reaction first explained by Wechselmann[6] in connection with intravenous salvarsan administration, and shown to be due to a

fungous growth in supposedly sterile, distilled water after it has stood for several days. In this case, No. 63, donor and recipient both received normal saline intravenously, as is frequently necessary in the syringe cannula method. The saline had been prepared from water distilled several days before. Immediately after the transfusion both donor and recipient experienced a severe chill, with a rise of temperature to 103°, nausea and vomiting. Their temperatures did not reach normal until three days after the transfusion. Since then only water distilled on the day of the transfusion has been used either for administration to the patient as saline or citrate solution intravenously, or in the preparation of the apparatus. Although some of the transfusions by the syringe cannula method preceding this one may have been followed by a water reaction, it is probably a negligible factor in the total percentage of reactions, since in subsequent transfusions by the syringe cannula method, when only freshly distilled water was used, 67 per cent. of the cases still had reactions. It is therefore evident that the method of transfusion has nothing to do with the production of a reaction.

III. *The Relation of Blood Relationship to the Reaction.* Table V shows the relative frequency of reactions in cases where donor and recipient were or were not blood relations.

TABLE V.

Blood relationship.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Yes	40	24	60
No	236	155	66
Not recorded	4		

With such a comparatively small number of blood relations in the series, this difference of 6 per cent. is negligible, and it is evident that, so far as liability to reaction is concerned, blood relationship is of no advantage in procuring the best possible donor for a patient.

IV. *The Relation of Blood Groups to the Reaction.* Table VI shows the relative number of reactions in the different blood groups.

TABLE VI.

Blood group.	Number of transfusions.	Number of reactions.	Percentage of reactions
I	123	83	68
II	68	44	65
III	36	24	66
IV	1	1	100
Not recorded	52		

In the three common groups, and probably in Group IV also, there is practically no difference in the relative compatibility of

the blood of individuals within each group. The factor of incompatibility which is responsible for reactions in cases which have been properly grouped is therefore something which is not detected by the ordinary method of testing for agglutination and hemolysis.

V. *The Relation of the Amount of Blood Given to the Reaction.* Table VII shows the relative frequency of reactions following transfusions of large and small amounts of blood.

TABLE VII.

Amount of blood.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Less than 200 c.c.	11	1	9
More than 200 c.c.	260	175	67
Not recorded	9		

Among the transfusions of more than 200 c.c. the percentage of reactions from transfusions of 300 c.c., 400 c.c., 500 c.c., etc., is fairly uniform, which warrants their being grouped together. Although the number of transfusions of less than 200 c.c. is too small to be very conclusive, nevertheless the contrast in the percentage of reactions is very striking, and it is possible that reactions could be practically eliminated if amounts of 200 c.c. or less were given frequently, rather than larger amounts at greater intervals.

VI. *The Relation of Subsequent Transfusions to the Reaction.* This refers to all transfusions administered to one patient from any donor. The greatest number of transfusions given to one patient in this series was 23, which were donated to a case of pernicious anemia. Five different donors were used, one as many as nine times. Table VIII shows the increase of reactions in subsequent transfusions.

TABLE VIII.

No. of the transfusion.	Number of transfusions.	Number of reactions.	Percentage of reactions.
1st	99	60	60
2d	53	31	59
3d	33	22	67
4th	25	17	68
Over 4th	70	52	74

At first the increase in percentage of reactions with subsequent transfusions does not appear striking, but when it is remembered that the patients who receive the larger number of transfusions are usually those whose condition ultimately becomes poorer, and their power of reaction therefore less, the figures are more conclusive. It would seem, therefore, that there is a tendency for an increase in the liability to reaction with subsequent transfusions.

VII. *The Relation of Subsequent Donation to the Reaction.* This refers to the number of times the same donor was used for a single recipient. The largest number of donations in this series by a single donor to a single recipient was 9, the case mentioned above. Table IX shows the increase in reactions with subsequent donations.

TABLE IX.

Number of the transfusion.	Number of transfusions.	Number of reactions.	Percentage of reactions.
1st	184	105	57
2d	40	28	70
3d	22	16	73
4th	11	10	91

Beyond the fourth donations the figures are too small for a fair comparison. It is evident from this table that subsequent donation tends to increase the frequency of reaction. The tendency to post-transfusion reaction may therefore be lessened by using different donors in cases which need many transfusions.

VIII. *The Tendency for Individual Donors to Cause Reactions.* Of the 108 donors used in this series, 6 were used twelve or more times, and therefore offer enough statistics from which to draw conclusions as to their tendency to cause reactions. This is shown in Table X.

TABLE X.

Donor.	Number of transfusions.	Number of reactions.	Percentage of reactions.
J. K.	36	28	78
H. T.	16	14	88
C. J.	16	12	75
E. D.	15	11	73
C. C.	15	7	47
A. A.	12	6	50

Fifty per cent. of J. K.'s donations and 62 per cent. of H. T.'s were followed by reactions with a temperature of 102° or over. These are in contrast to the last two, C. C. and A. A., only 33 per cent. of their donations being accompanied by a temperature of 102° or over. There is therefore considerable difference between donors in their tendency to cause reactions.

POST-TRANSFUSION LEUKOCYTOSIS. The similarity of some of the post-transfusion reactions to those caused by the intravenous administration of typhoid vaccine,[7] in which there was a marked transient polymorphonuclear leukocytosis, led us to follow closely the white blood cells in a few cases during their post-transfusion reactions.

CASE 224.—Pernicious anemia: In good condition, was given 600 c.c. of blood by the citrate method. Blood count before transfusion showed red blood cells 1,066,000, hemoglobin 45 per

cent. The next day red blood cells 1,760,000, hemoglobin 53 per cent. Transfusion was followed by a chill and temperature of 104.2°. White blood cells changed as follows:

Before transfusion, white blood cells	5,300,	polynuclears 59 per cent.
Three hours after transfusion, white blood cells	8,500,	"	83	"
Seven hours after transfusion, white blood cells	11,600,	"	80	"
Fifteen hours after transfusion, white blood cells .	27,000		
Seventeen hours after transfusion, white blood cells	19,500,	"	81	"
Nineteen hours after transfusion, white blood cells	15,600		
Twenty-three hours after transfusion, white blood cells	13,800,	"	82	"
Twenty-seven hours after transfusion, white blood cells	9,700,	"	81	"

One week later red blood cells were 1,800,000, hemoglobin 64 per cent., and the patient was discharged much improved after a second transfusion a week later, with red blood cells 2,100,000, hemoglobin 66 per cent. This was evidently a case in which spontaneous remission was possible.

CASE 270.—Diabetes and metrorrhagia: In good condition; was given 500 c.c. of blood by the citrate method. Before transfusion red blood cells 3,300,000, hemoglobin 30 per cent. Ten days after transfusion red blood cells 4,600,000, hemoglobin 55 per cent. Transfusion was followed by a chill lasting twenty-five minutes, with nausea and vomiting and a rise of temperature to 103.8°, falling gradually to 99.4° twenty-three hours after transfusion. The white blood cells changed as follows:

Before transfusion, white blood cells	5,400,	polynuclears 54 per cent.
One-quarter hour after transfusion, white blood cells	6,100,	"	70	"
Two hours after transfusion, white blood cells .	6,300		
Five hours after transfusion, white blood cells .	14,300,	"	91	"
Seventeen hours after transfusion, white blood cells	9,000,	"	85	"
Twenty-four hours after transfusion, white blood cells	5,300,	"	82	"
Twenty-nine hours after transfusion, white blood cells	5,200,	"	88	"

Dilatation and curettage was performed six weeks after transfusion and patient was discharged, with red blood cells 4,460,000 and general condition greatly improved.

CASE 185.—Pernicious anemia: In good condition; was given 275 c.c. of blood by the citrate method. Before transfusion red blood cells were 920,000, hemoglobin 36 per cent. Twenty-four hours after transfusion red blood cells 900,000. One week later red blood cells 1,030,000, hemoglobin 25 per cent. Transfusion was followed by a chill lasting twenty minutes, and temperature

reached 105° five hours later and then fell rapidly to 100° seven hours after transfusion. White blood cells changed as follows:

Before transfusion, white blood cells	5,200, polynuclears 62 per cent.
One-quarter hour after transfusion, white blood cells	5,870
Three hours after transfusion, white blood cells	4,150
Six hours after transfusion, white blood cells .	4,000
Fourteen hours after transfusion, white blood cells	4,800

This patient was in the hospital two and a half months and received five transfusions, but his red blood cells never exceeded 2,300,000. He was apparently a case without the power of spontaneous remission.

CASE 230.—Pernicious anemia: In good condition; was given 350 c.c. of blood by the citrate method. Before transfusion red blood cells were 850,000, hemoglobin 30 per cent. Twenty-four hours after transfusion red blood cells 1,660,000, hemoglobin 33 per cent. Three days later red blood cells 1,490,000, hemoglobin 33 per cent. Three weeks later red blood cells had again fallen to 826,000, hemoglobin 20 per cent. Following transfusion the patient had a chill and the temperature rose to 103.6° two hours later, falling gradually to 98.6° twenty hours after transfusion. White blood cells changed as follows:

Before transfusion, white blood cells	2,800, polynuclears 34 per cent.
Two hours after transfusion, white blood cells . .	1,400
Three hours after transfusion, white blood cells .	1,200
Six hours after transfusion, white blood cells . .	1,800
Sixteen hours after transfusion, white blood cells .	2,800
Twenty-eight hours after transfusion, white blood cells	2,800

This patient had nine transfusions, but his red blood cells never exceeded 2,200,000, and he died two and a half months after his first transfusion. He was another case without the power of spontaneous remission.

The absence of leukocytosis in the last 2 cases is in accordance with the failure of their blood to recuperate when stimulated by transfusion. In the same type of case an absence of leukocytosis is also seen in the presence of acute infection. In fact, Case 185, after a subsequent transfusion, developed facial erysipelas, and during the course of that infection his white blood cells never rose above 9100, with 65 per cent. polymorphonuclear leukocytes. A further study of the white blood cells during post-transfusion reactions in cases other than pernicious anemia, might show a constant occurrence of leukocytosis similar to that following the intravenous administration of a foreign protein.

DISCUSSION OF REACTIONS. There are several possibilities as to the main cause of the post-transfusion reaction. These possibilities are: (1) The water used in preparation of the apparatus or

in the saline or citrate solutions; (2)· impurities in sodium chloride or sodium citrate used; (3) hemolysis or agglutination of red blood cells; (4) trauma to the red blood cells by manipulation, with resultant hemolysis; (5) a change in the plasma protein by its contact with a foreign substance; (6) the interaction of plasma ferments with the partial splitting of the foreign protein introduced; (7) the presence of antibodies in the recipient's blood which split up the foreign protein introduced. These will now be considered one at a time.

1. Water distilled on the day it is used has been shown to be uniformly incapable of causing febrile reactions and can therefore be eliminated as a factor.

2. The use of chemically pure salts should free them from suspicion as factors in causing a reaction. Moreover, one would expect more uniformity in the occurrence of the reaction if the salts were a factor. That the amount of sodium citrate administered had nothing to do with the occurrence of the reaction is shown by Table XI, which shows the amount of citrate and the corresponding reactions in the 119 cases where the amount given is stated in our records.

TABLE XI.

Grams of citrate.	Number of cases of no reaction.	Number of cases of first-degree reaction.	Number of cases of second-degree reaction.	Number of cases of third-degree reaction.
0 to 1	1	4	2	4
1 to 2	11	6	8	4
2 to 3	25	10	23	8
3 to 4	4	2	4	2
4 to 5	0	0	0	0
5 to 6	1	0	0	0

The case receiving the largest amount of citrate had no reaction. Furthermore, the occurrence of as high a percentage of reactions by the syringe cannula method as by the citrate method eliminates this factor.

3. Lindemann[8] ascribes the reaction solely to the intravascular occurrence of hemolysis, comparing it to the chill and fever in malaria at the time of the bursting of the red blood cells, liberating the organism, and he states that very careful grouping of donor and recipient can eliminate hemolysis. In his series of 155 transfusions, in which he personally supervised the selection of donors in all except 9 cases, there occurred 21 cases of a rise of temperature of 2° or over which are not explained unless hemolysis occurred *in vivo* but not *in vitro*. This, of course, is possible, and if so, would be impossible to eliminate.

Brown[9] showed that the malaria pigment liberated at the time of the bursting of the red blood cells is hematin. By injecting this substance into animals[10] he produced a febrile paroxysm similar to the malarial paroxysm.

It is well known that in paroxysmal hemoglobinuria the attacks are accompanied by a chill and febrile reaction very similar to that following transfusion. Hoover and Stone,[11] in a study of 2 cases of this disease, found a marked polymorphonuclear leukocytosis accompanying the attacks, which is similar to that we have shown above with post-transfusion reactions. They also claim that the only blood pigment found in the blood plasma at the time of the attack is oxyhemoglobin.

The examination of the urine to detect the presence of marked blood destruction *in vivo* might be expected to throw some light on the relation of blood destruction to the post-transfusion reaction. In malaria the paroxysm is followed by an abundance of urobilin in the urine. In paroxysmal hemoglobinuria the disease takes its name from the excretion of large amounts of hemoglobin in the urine. In our series of transfusions, however, the relation of the reaction to the excretion of urobilin and hemoglobin is by no means definite. Table XII shows this relation in cases in which the urine was examined after transfusion.

TABLE XII.

	No reaction.	First-degree reaction.	Second-degree reaction	Third-degree reaction.
		Number of cases of		
Urobilin absent	18	19	32	11
present	5	9	5	2
Hemoglobin absent	27	25	36	16
present . . .	3	2	7	3

It will be seen that in cases of even severe reaction, both urobilin and hemoglobin were absent in the large majority of cases after transfusion. Furthermore, as urinary tests for these substances were not made before transfusion, urobilin may have been present in some cases before as well as after transfusion, as it frequently is in pernicious anemia. This source of evidence of blood destruction as the cause of the post-transfusion reaction therefore seems very small. Hemolysis cannot, however, be disregarded as the possible cause of some of the reactions.

The occurrence of a slight amount of agglutination of transfused cells after proper grouping of donor and recipient is also a possibility, the presence of which would be very difficult to determine. A very careful examination of the recipient's blood during the reaction would be necessary, which was not done in any case in our series.

4. Trauma to the red blood cells by manipulation during the transfusion may be excluded as a possible cause of the reaction, since the amount of trauma is practically uniform in all transfusions by a single method, while the occurrence of the reaction is far from uniform. Moreover, in the cases in our series where defibrinated blood was used, in which method there is undoubtedly more trauma to the red blood cells than by the other methods, no reactions occurred.

5. The change of plasma protein by its contact with glassware, metal and rubber tubing can also be eliminated because of the lack of uniformity of the occurrence of the reactions, under similar methods of treating the blood.

6. The production of the reaction by the partial splitting of the foreign protein introduced, with the formation of a toxic product, either by the interaction of plasma ferments or by the presence or acquisition of antibodies in the recipient's blood, takes us into a field which has as yet been but slightly investigated. There are several points in our findings, however, that suggest that the post-transfusion reaction may be one of this type. The reaction in most cases is, of course, much less severe than the typical foreign protein reaction, but as the protein introduced is only slightly, if at all, different from the recipient's plasma, a reaction of extreme grade would not be expected. The absence of a reaction with small amounts of blood, the progressive increase of reaction with subsequent transfusions, and especially with subsequent donations by the same donor, the tendency of some donors to cause more reactions than others, and the occasional occurrence of transient polymorphonuclear leukocytosis, all tend to support this view. No more definite conclusions can be drawn on this point until the subject has received much more detailed study.

CONCLUSIONS. 1. Transfusion is of real value in cases of hemorrhage, in clean operative cases, in pernicious anemia, and in some secondary anemias. It is of little or no value in septic operative cases, cases of bacteriemia, or cases of acute leukemia.

2. The sodium citrate method of transfusion is a very simple and satisfactory method. A dilution of citrate up to 0.5 per cent in 1000 c.c. of blood can be used without producing toxic symptoms in an adult, and that dilution prevents clotting better than a dilution of 0.2 per cent.

3. Blood grouping should always be carried out before a transfusion. Where a reliable laboratory is at hand the direct grouping of donor and recipient is not necessary, but otherwise should always be performed. Failure to determine the compatibility of the bloods may result in the sudden death of the patient.

4. Post-transfusion reactions occurred in 63.6 per cent. of the cases in our series, the reactions varying greatly in degree, but all being evidenced by a rise of temperature to 100° or more.

5. The recipient in good general condition is much more likely to have a reaction than the one in poor condition.

6. The method of transfusion, the blood relationship of donor and recipient, and the blood group of the recipient seem to have nothing to do with the occurrence of the reaction.

7. Transfusions of small amounts of blood, i. e., less than 200 c.c., are less likely to be followed by reactions than are transfusions of larger amounts.

8. The more transfusions a patient is given the more likely he is to have a reaction, especially if the same donor is used a large number of times. The blood of some donors is more likely to cause reactions than the blood of others.

9. In some cases the post-transfusion reaction is accompanied by a marked polymorphonuclear leukocytosis. Whether this is due to intravascular hemolysis or to the formation of a toxic product from the partial splitting of a foreign protein cannot at present be stated. It seems most likely, however, that one of these phenomena is probably responsible for most post-transfusion reactions.

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MENINGITIS SYMPATHICA.[1]

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MENINGITIS sympathica, so named by Plaut and Schottmüller,[2] is a condition of the cerebrospinal fluid caused by inflammation in the neighborhood of the meninges: (1) It is characterized by an increase in the pressure of the fluid, which sometimes registers as high as 400 mm. in the Strauss[3] lumbar-puncture instrument. (2) There is generally a considerable or moderate increase of the albumin content and cellular elements. The cells are usually polymorphonuclear leukocytes, but occasionally they are lymphocytes. (3) The fluid, which may be clear or turbid, is sterile. (4) There may be symptoms of meningitis.

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[1] A part of the subject matter of this paper was read at the meeting of the American Association of Neurologists in New York.
[2] Leitfaden zur Untersuchung der Zerebrospinalflussigkeit.
[3] Jour. Am. Med. Assn., lxii, 1327.

Brain abscess is one of the most frequent causes of meningitis sympathica, and the latter condition may be of great assistance in the diagnosis of the former. This is especially true of cases in which there has been a previous otitic inflammation with or without mastoid or lateral sinus involvement. The following case is an illustration:

CASE I.—A. F., admitted to the service of Dr. Whiting, December 1, 1912, with the diagnosis of mastoiditis. The following day 12 c.c. of cloudy spinal fluid under increased pressure was removed. This fluid showed an increase in albumin content and an increased number of leukocytes and sugar reduction. Cell count: polymorphonuclear, 91 per cent.; mononuclear, 9 per cent. Fluid sterile. Operation for mastoiditis. Lateral sinus exposed and found clear. The dura opened, but no meningitis was discovered. Subsequently, rigidity of the neck and marked Kernig developed. Blood cultures were found sterile; the jugular was exposed and tied. At the same time a right external rectus palsy developed. Cerebellum aspirated after death and a large quantity of pus obtained.

In this case the presence of meningitis sympathica pointed to the presence of intracranial suppuration and warranted further exploration at the time of the first operation.

The following history is unique in that the meningitis sympathica was due to an abscess in a tumor adjacent to the brain:

CASE II.—E. H., admitted February 11, 1911. Illness began five days ago with peritonsillar abscess, which ruptured spontaneously thirty-six hours before admission. Patient was suddenly seized with a severe chill and vomiting. Twelve hours before admission became comatose.

Physical Examination. Patient comatose; temperature, 106° F. Marked rigidity of neck; cheeks flushed; breathing deep and stertorous. Right pupil larger than left. Shrapnell's membrane congested in left ear, otherwise ears were negative. Babinski and Kernig signs present.

February 11, 1911. Spinal fluid shows 100 per cent. polymorphonuclears and an absence of bacteria, indicating presence of a meningitis sympathica. Patient continued to have temperature up to 106.6° F. Rigidity disappeared, also Kernig's sign. Breathing labored and stertorous. Pupillary reflexes lost. Pulse became very slow and died.

Autopsy. Brain: On the left side of the sella turcica was a soft, grayish-red tumor mass about the size of a peach-stone, which had forced the optic chiasma and the corpora mammillaria to the right. Extending forward from this tumor mass, and seemingly continuous with it, was a cystic mass lying in a pit on the inferior surface of the posterior part of the left olfactory lobe. When this cyst was opened, thin yellow pus exuded. The convolutions of the brain were flattened and the surface was congested.

Diagnosis. Meningitis sympathica; infected tumor of the hypophysis; peritonsillar abscess.

Occasionally a brain abscess may be present, associated with a marked meningitis over the convexity of the hemispheres, which gives rise to a meningitis sympathica. The spinal fluid contains no demonstrable bacteria. The presence of such an extensive process cannot be diagnosed.

CASE III.—A. C., admitted November 28, 1910. For two weeks before the present illness patient had occasional abdominal pains. Five days before admission had severe abdominal pains and headache. Vomited once the day before admission. Strabismus, rigidity of neck, and flatness of one side of the face were noted the day before admission. Involuntary urination and defecation. For two days before admission had not spoken; lies quietly unless disturbed. No ear discharge.

November 29. Patient stuporous but can be aroused. Cheeks flushed; lips red; MacEwen sign present, together with marked rigidity. Eyes: Left external rectus palsy; pupils equal and regular; contracted; react to light; fundi show marked edema of both optic nerves, more on the right side; veins engorged; retina cloudy; no hemorrhages. Extremities: No palsies; reflexes active. Abdominal reflexes diminished on the right side; marked Kernig. Slight hyperesthesia of right arm and chest. Von Pirquet negative. Spinal puncture yielded 30 c.c. of cloudy fluid under tension. Spreads of cerebrospinal fluid negative for bacteria. Smears show almost entirely polymorphonuclear leukocytes; 30 c.c. of Flexner's serum introduced. Patient semiconscious; does not speak.

November 30. During the morning patient had Jacksonian epileptiform seizures limited to right side of face and arm and occasionally involving the right leg. Attacks every ten to fifteen minutes.

November 30. 9 P.M., 40 c.c. of fluid removed under a pressure of 210 mm. 11 P.M., sudden attack of cyanosis and heart failure, with death.

Autopsy. Brain: Very recent brain abscess formation in the cortex, with a perivascular infiltration of polymorphonuclear and mononuclear leukocytes in the vessels in the neighborhood of the abscess. Thick, greenish-yellow pus covered the convexity of the brain, but most marked in quantity over the left hemisphere, principally in the motor region. The pus was also present over the cerebellum, the base of the brain, and the pons and upper cord. It had collected under the pia in the interpeduncular space. The pia everywhere was markedly congested. The fluid in the lateral ventricles were moderately turbid. There was a small abscess of recent origin in the right lateral lobe of the cerebellum.

Wolf[4] reports a case in which turbid spinal fluid was sterile and

[4] Cited by Koerner: Die Ohrenheilkunde der Gegenwart und ihre Grenzgeb.

contained numerous red cells and leukocytes. The autopsy showed an uncomplicated abscess in the temporal lobe. In discussing this case, Leutert assumed that a healed miningitis was responsible for the changes in the spinal fluid, but such an hypothesis is unnecessary because meningitis sympathica occurs without any inflammatory process in the meninges.

Ruprecht[5] reports an autopsy in a case of uncomplicated abscess of the temporal lobe in which cloudy spinal fluid under increased tension was obtained before death. It contained a sediment of polymorphonuclear leukocytes and no bacteria either in smears or cultures.

Meningitis sympathica may be the forerunner of a developing meningitis purulenta and therefore its early recognition is of great importance. This is specially true in those cases in which the clinical symptoms of the meningitis are more prominent than are those of the brain abscess.

CASE IV.—A child, aged two years, was kicked by a horse and received a scalp wound on the right side of the forehead. It was not unconscious and there were no symptoms of increased intracranial pressure. It had had high fever nightly for some time before admission to the hospital and had lost weight. Examination revealed a depression over the right frontal bone, rigidity of the neck and slight Kernig. Thirty c.c. of slightly turbid fluid under considerably increased pressure was obtained by lumbar puncture. The fluid showed increased albumin content and cell increase, but the mononuclear leukocytes were 99 per cent. and the polymorphonuclear leukocytes only 1 per cent. The fluid was sterile. Six days later a second puncture gave a similar result. On the succeeding day a craniotomy revealed a subdural abscess underneath the depressed bone. Seven days later, the child not improving, a third lumbar puncture yielded cloudy fluid under very high pressure. This fluid now showed an increase in the number of cells, all polymorphonuclear and streptococci in culture.

The meningitis sympathica had changed into a meningitis purulenta and the child died. Had the significance of the meningitis sympathica been recognized the operation for cerebral abscess could have been performed at once with greater possibilities of therapeutic success. The following case illustrates this point:

CASE V.—Admitted to the service of the late Dr. Gruening, complaining of pain in the left ear and left hemicranium. Twenty c.c. of turbid fluid was obtained. The cells, increased in number, showed 84 per cent. polymorphonuclear and 16 per cent. mononuclear leukocytes. No bacteria present. Radical mastoid operation performed. The dura exposed and found to be pulsating, but covered with a layer of greenish-colored fibrin. Upon exploration a large epidural abscess containing foul-smelling, greenish pus was

discovered and evacuated. Four days later clear fluid was obtained under normal pressure. The patient made an uneventful recovery.

The presence of the turbid spinal fluid undoubtedly prompted the operator to explore beyond the mastoid in this case. It is furthermore important to note that the abscess was an epidural one, and yet by its irritation gave rise to the meningitis sympathica.

It occasionally happens that meningitis sympathica may be present and yet cause no symptoms. Its early recognition is always important, not only because of the prognosis but also of its bearing upon the treatment. In fact, I feel that an examination of the spinal fluid should be made in every case of mastoiditis before operation.

At times an old middle-ear infection may cause an epidural inflammation by extension. The mastoid symptoms may be absent but the meningitis sympathica indicates a suppurative focus near the meninges. The following case is one in which the surgeon was probably led to radical exploration by its presence:

Case VI.—D. B., admitted July 27, 1908. Discharge from both ears in childhood. Present illness began, with sudden severe pain in the left mastoid region. No discharge. Fever and chills.

July 27. Physical examination: Right ear: shows moderate granulations. Left ear: the upper and outer part of the middle ear filled with cholesteatomatous material. No edema. Marked tenderness over the mastoid. Eyes: veins of both fundi are dilated. Neck: rigid and head retracted. Marked Kernig sign. Pulse: 58 to 60. Lumbar puncture: 20 c.c. of turbid fluid under increased tension. Fluid contained leukocytes and no bacteria. Diagnosis lay between sinus thrombosis or a suppurative process near the meninges. Operation: Dr. Koller. Dura found pulsating and covered with greenish fibrin. Flow of blood free from sinus. No thrombosis. Sinus packed with gauze.

July 30. Temperature dropped to 100° F.

July 31. Lumbar puncture: 30 c.c. of clear fluid under normal tension.

August 5. Temperature normal. Slight rigidity of neck; slight Kernig sign. Sinus wound healthy. Upon removing drainage tube a fairly large quantity of cerebrospinal fluid discharged.

August 11. Opening closed. Headache which existed for last few days had ceased. Uneventful recovery.

This was a case in which the absence of bacteria in the blood pointed against sinus thrombosis and the sterile spinal fluid against a suppurative meningitis.

Grossman[6] reports a case which is interesting because the meningitis sympathica appeared after the mastoiditis had been cured.

[6] Arch. f. Ohrenheilk., vol. lxiv.

The autopsy revealed a thrombosis of the superior petrosal sinus and no meningitis. He considered the case one of so-called otitic sepsis.

The persistence of meningitis sympathica in a case in which there is a known suppurative intracranial focus, is almost positive indication that the focus has not been found and treated. The following case supports this assertion and furthermore demonstrates the possibility of the meningitis becoming a true infective process.

Case VII.—M. G., admitted August 12, 1908. Four years ago had pain in right ear. Drum incised. Ear discharged pus for three months. Six weeks ago had gangrenous appendicitis. Eight days before admission had profuse discharge from right ear. Two days later had severe headache. Temperature, 102° F. Prostrated; vomited several times. Marked rigidity of neck; herpes labialis. No chill; no pain over mastoid.

Physical Examination. Mastoids; no tenderness or swelling. Knee-jerks exaggerated. No clonus; no Babinski. Neck rigid. Kernig marked. Symptoms pointed to a meningitis which did not appear to be of the ordinary cerebrospinal type. Ear regarded as the probable cause. Lumbar puncture: 25 c.c. of turbid fluid under markedly increased tension. Polymorphonuclear, 80 per cent. No bacteria found. Aseptic polymorphonuclear meningitis was diagnosed and operation for brain abscess advised.

August 13. Operation: Dr. Wolff. Right mastoid cells were found practically sclerosed. Antrum exposed and found filled with a mass of cholesteatomatous material, as was also the middle ear. Sinus normal. Dura exposed and found pulsating. No epidural abscesses. It was not considered advisable to aspirate the brain at this time.

August 14. Pulse, 72 to 80; headache; less pain over right ear. Right facial palsy. Cerebrospinal fluid; 85 per cent. polymorphonuclear leukocytes.

August 15. Patient better. Much less headache; less rigidity of neck; Kernig less marked.

August 19. Some edema of the eyelids, especially the lower. Eye-grounds: edema; infiltration of both retinæ, especially on left side. Retinal vessels are raised and structure of retina looks blurred.

August 22. Eyes examined by Dr. Friedenberg. Pupils dilated. Right disk slightly hazy; veins tortuous; retina near disk slightly edematous. Slight pallor of temporal half of disk.

September 6. First dressing. Profuse discharge from mastoid. Since operation patient has had a temperature of 99° to 102° F. Patient has rigid neck and Kernig's symptoms.

September 7. Very profuse discharge. Wound still open.

September 12. Packing removed. Rigidity of neck and Kernig not so marked.

September 20. Lumbar puncture. Cloudy fluid; polymorphonuclear, 71 per cent.

September 22. Meningitis symptoms still marked. Lumbar puncture; 25 c.c. of turbid fluid withdrawn. Polymorphonuclear, 85 per cent. After each puncture the patient's symptoms were temporarily relieved.

September 24. Symptoms still present. Patient worse. Temperature, 103° F.; pulse, 80.

Exploratory Craniotomy. Dr. Oppenheimer; to locate focus. The dura under marked tension. Area of dura about the size of a 50-cent piece exposed. No pus or purulent cerebrospinal fluid escaped. With a scalpel, punctures of the brain were made in four or five directions, but each time with a negative result. Dura closed. Line of suture closed by Cargile membrane. Wound packed with iodoform gauze.

September 26. Following the operation the symptoms were more marked. Patient delirious. Lumbar puncture. Fluid under tension and almost pure pus.

September 27. Condition relieved after lumbar puncture. Rational a short time; ceased.

Note. The first cerebrospinal fluids contained no bacteria; when the patient became very sick again the fluid contained bacteria microscopically, but they would not grow. After the operation pure pus was found; it was considered probable that a brain abscess had ruptured.

Autopsy. At the apex of the petrous portion of the temporal bone there was an area of caries and necrosis. The pus was foul, thick, and greenish. It contained a variety of bacteria, most of which were Gram-positive bacilli. No abscess could be found anywhere in the brain, but the presence of practically pure pus in the cerebrospinal canal shortly before death shows that an abscess which was probably present previously had ruptured into the ventricle. The patient evidently had three attacks of so-called "meningitis sympathica." These were probably due to an infection of the canal by anaërobic bacilli which did not multiply sufficiently to cause progressive meningitis.

Meningitis sympathica may also be present in patients in whom there is an inflammation of the accessory sinuses of the cranium or even in the structures adjacent to it.

CASE VIII.—Patient suffering from orbital cellulitis of nine days' duration; admitted to the service of Dr. Elsberg November 29, 1913. Orbit incised and drained. The next day lumbar puncture; 15 c.c. of turbid spinal fluid under tension. Cells increased and all polymorphonuclear. The fluid contained a contaminating Staphylococcus albus. This finding means that there was a meningitis sympathica and that the inflammatory process or a toxin had reached the meninges.

Patient considerably improved by operation, and yet irritation of the meninges warned against a too hopeful prognosis. Thirteen days following the operation, although the patient was doing well, I requested another lumbar puncture; 20 c.c. of slightly turbid fluid under a pressure of 160 mm. obtained. It contained 133 cells to the cubic millimeter, with a greater proportion of mononuclear than polymorphonuclear leukocytes. Albumin content increased. Cultures sterile. These findings were a positive indication that the patient was not out of danger.

Patient left hospital apparently cured December 30, 1913.

March 10, 1914 (three months after discharge), readmitted because of severe headaches in the right temporal region. No evidence of accessory sinus disease. Eye examination negative. Lumbar puncture: clear fluid under increased tension, but without an increase of cells. Patient discharged with the diagnosis of periostitis of the frontal bone.

June 25 (three months after his second discharge), readmitted because of severe headaches in the same region as previously. Drowsiness and vomiting; symptoms of intracranial pressure. After admission he had a convulsion. Lumbar puncture: fluid under pressure, with increased albumin content, increase of polymorphonuclear leukocytes, and no bacteria. This was evidence of renewed meningeal irritation. Operation: frontal lobe exposed. It appeared soft and the pia over it was edematous, but no abscess was found.

August 20. Discharged, improved.

He was subsequently admitted to another hospital, where repeated lumbar puncture yielded sterile turbid spinal fluid. A diagnosis of brain abscess in the right frontal lobe was made and the lobe explored, but without result. Autopsy revealed an abscess in the lobe.

This case therefore shows how an inflammation which in the beginning is not intracranial may cause meningitis sympathica and that the latter's presence may be of great importance in determining the prognosis and the treatment.

Reischig[7] reports a case of meningitis sympathica dependent on suppuration in the anterior sphenoidal cells under the name of meningitis aseptica.

Meningitis sympathica is of clinical significance when it occurs in association with a known or suspected intracranial suppurative condition. It is very difficult, if not impossible, to differentiate it occasionally from the condition known as meningitis aseptica. In this latter disease the spinal fluid possesses the same characteristics as the fluid in cases of meningitis sympathica, except that it may be more turbid and contain a greater number of leukocytes. The

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[7] Zeit. f. Ohrenheilk., 1913, Bd. 69, p. 78.

differential diagnosis between the two depends upon the presence or absence of a possible inflammatory cause. It is probable that many of the reported cases of meningitis aseptica were really cases of meningitis sympathica and that they recovered without discovery of the primary suppurative condition in the brain or adjacent structures.

One of the most recently reported cases of this class, namely, that of Zabel,[8] is not a case of meningitis aseptica, but primarily one of subarachnoid hemorrhage in which the secondary reaction of the meninges was evidenced by an accumulation of leukocytes which caused a turbid fluid. In many of the cases there is a history of trauma which may precede the development of the meningitis by as much as a year. Some of these cases apparently recover and leave the suspicion that there may be a latent abscess remaining.

There is also some question in both meningitis sympathica and meningitis aseptica whether bacteria may not at some time have been present in the spinal fluid. Occasionally meningococci cannot be found in spreads or grown in cultures from the spinal fluid; especially in old or subacute cases of meningitis. Concetti, Oseki and others believe that bacteria are destroyed by the spinal fluid for a time or else lie in the meninges. This may account for the number of cases in which Mygind[9] found an extensive meningitis at autopsy and yet could find no organism in the spinal fluid during life. He reports 24 sterile fluids out of 61 clinical cases of meningitis. In 12 of the 24 cases the presence of meningitis was confirmed by autopsy.

Widal has pointed to changes in the cells in the spinal fluid as a means of differentiation between the septic and aseptic meningitis. In the septic meningitis the leukocytes give evidence of necrobiosis. There is destruction of the nuclei, degeneration of the cell borders, with the disappearance of the granules and the appearance of the vacuoles.

In aseptic meningitis and meningitis sympathica the cells are unaltered. In long-standing cases of these two conditions there are some changes in a few cells at a time and lymphocytes very frequently replace the polymorphonuclear leukocytes.

Cerebral syphilis occasionally presents the clinical picture of a meningitis and a very turbid spinal fluid containing a large number of leukocytes. Belin and Bauer report a case in which the fluid remained turbulent for four months; Revaut, one of two months; and Widal and Lemierre two of a few days' duration. Of course in such cases the history of syphilis and the positive Wassermann reaction aid in the differential diagnosis.

The differential diagnosis between meningitis sympathica and tuberculous meningitis is most important. When there is a known

8 Ztschr. Ohrenheilk., 1914–15, Bd. 72, p. 73.
9 Ztschr. Nervenheilk., 1910, Bd. 40.

focus of infection the diagnosis is not difficult, but occasionally cases are met with in which there may be considerable difficulty. As a rule the cell content in the spinal fluid in tuberculous meningitis is not increased in the early stage, and if it is the mononuclear leukocytes are predominant. But there are exceptions to this. An example of the difficulty of differential diagnosis is seen in the following case:

CASE IX.—A child, aged fourteen months, was admitted to Dr. Elsberg's service in stupor, with the history of having a discharging ear two weeks previously. The child had no symptoms of meningitis, but there was a spastic hemiplegia. Lumbar puncture: fluid under pressure; 200 cells per cubic millimeter; 15 per cent. mononuclear. This cell count in itself did not indicate a suppurative intracranial process. Fluid: bacteria-free; no tubercle bacilli found. Exploration of the brain, without results. The autopsy revealed a tubercular process in the interpeduncular region.

The cerebrospinal fluid of acute poliomyelitis during epidemics is under increased pressure and contains a marked increase of cellular elements during the acute febrile period. The increase generally takes place in the polymorphonuclear leukocytes, which in some instances have been observed to be as numerous as 3000 per cubic millimeter. The fluid may be very turbid and is always sterile. In the subsiding stage there is a decrease in the number of cells with the lymphocytes predominating. In addition there are present the symptoms of meningitis. The picture therefore is one of meningitis sympathica. The diagnosis, of course, depends upon the association of the meningitis with the other symptoms characteristic of the disease, except in the abortive cases, in which the findings in the spinal fluid furnish the only definite evidence of the disease.

Polioencephalitis inferior of infectious origin may cause a meningitis sympathica, as the following case shows:

CASE X.—April 14, 1913, a patient was admitted to Dr. Gerster's service suffering from an ischiorectal abscess. He was discharged in thirteen days, cured. Six weeks later he was readmitted with high fever; complete right facial paralysis; right external rectus paralysis; horizontal nystagmus; and left internal rectus paresis. No rigidity of the neck. Lumbar puncture: turbid fluid under increased tension with a great increase of polymorphonuclear. Cultures and spreads were negative. A diagnosis of abscess in the right side of the posterior fossa was made and an operation performed, with a negative result. The autopsy revealed a polioencephalitis, with softening involving the right half of the medulla.

In this case there was a focus of infection, and all the clinical symptoms pointed to the presence of an abscess as the most probable cause. Unfortunately, we frequently meet with intracranial inflammatory conditions in which there is no evidence of meningeal

irritation, but when meningitis sympathica is present it aids us both in the diagnosis and the treatment of such conditions.

The picture of meningitis sympathica may be present in cases in which there has been a subarachnoid hemorrhage, and enough time has elapsed to allow for the disappearance of most of the red blood cells. The reaction of the meninges in these cases is shown almost invariably by a very marked increase in the lymphocytes, and if the fluid does not show the presence of red cells the origin of the lymphocyte content is suggested by the peculiar yellowish tint of the fluid. This color is always diagnostic of hemorrhage unless there is reason to suspect a tumor or obstructive inflammatory lesion in the neighborhood of the spinal cord.

In cases of brain tumor in which there is an extreme degree of internal hydrocephalus, rigidity of the neck and Kernig's symptoms may occasionally be present. I have seen such a case in which, in addition, the spinal fluid was turbid and contained lymphocytes in excess. The tumor was situated in the thalamus and a hemorrhage had occurred in it directly under the ependyma of the lateral ventricle. This probably caused the lymphocytosis.

From the cases cited the difficulties of differential diagnosis of certain intracranial inflammations is only too apparent, but the finding in the spinal fluid of the properties characteristic of meningitis sympathica contributes a valuable aid for diagnosis, prognosis, and treatment.

I desire to express my indebtedness to the various attending physicians of the Mt. Sinai Hospital for permission to refer to their cases, and to Dr. E. Libman for his kind assistance and valuable suggestions.

REVIEWS .

THE third volume of this well-known and widely read review of medical progress appeared in September. Dr. William Ewart opens with an article of 77 pages on diseases of the thorax, heart, lungs, and bloodvessels. His article takes up in turn the recent literature on the respiratory function, to which he devotes 11 pages, and elaborates on the experiences gained in the present war on this subject. He then discusses the physical signs and methods of pulmonary tuberculosis, respiratory affections, pulmonary and bronchial blood functions and blood poisons, and the pericardium and heart, and the articles closes with a discussion of the recent advances in our knowledge of diseases of the thorax and its viscera.

Dr. William S. Gottheil's article on dermatology and syphilis is very interesting, showing, as it does, the recent strides made in our knowledge of autoserotherapy, the use of radium, and the various vaccines.

Edward P. Davis devotes 84 pages of the volume to his specialty, obstetrics, 34 of which are taken up with a discussion of the literature on pregnancy. This is followed with the views of various writers on the use of analgesia and anesthesia in obstetric practice. He then discusses the vaccine treatment of puerperal fever and the various advances made in the management of the puerperal period, and closes his article with an interesting discussion of the literature on the newborn.

Dr. William G. Spiller contributes the last article, on diseases of the nervous system, which is one of the most interesting in the volume. On the whole this number for September compares favorably with those in past years. S. S.

MEDICAL CLINICS OF CHICAGO. January and March, 1917. Pp. 231 and 237. Figs. 19 and 40. Philadelphia and London: W. B. Saunders Company, 1917.

THESE two numbers maintain the reputation which the excellence of the former ones has made for the series. In the January number appears a very encouraging clinic on splanchnoptosis, with accompanying skiagrams by Dr. Charles Spencer Williamson. Dr. Frederick Tice presents patients illustrating pericardiomediastinitis, pulmonary abscess, rectal stricture, abdominal aneurysm, and amebic dysentery. A clinic upon acidosis is covered by Dr. Frank Wright, including a discussion of the newer methods for detecting the condition. Dr. Walter W. Hamburger, in a discussion of achylia gastrica, emphasizes the similarity of the pains in this affection to those of hyperacidity. Dr. Ralph C. Hamill contributes two very interesting chapters, one upon certain psychiatric problems, especially neurasthenia, and the other upon acute disseminated myelitis and acute syphilitic meningomyelitis. In subsequent chapters Dr. M. Milton Portis deals with rectal carcinoma, Dr. Solomon Strouse with early pulmonary tuberculosis, alluding especially to the value of the roentgen rays, Dr. Charles Louis Mix with gastric and duodenal cases, Dr. Isaac A. Abt with disease resistance in relation to the nutrition of infants and with decomposition, the final ones being devoted respectively to barium diagnosis by Dr. James T. Case and purpura hemorrhagica by Dr. Arthur F. Beifeld.

The March number also presents clinics of Drs. Tice, Abt, Williamson, Hamill, Beifeld, Strause and Mix. Dr. Herman L. Kretschmer discusses the fulguration treatment of bladder papillomata, which is more properly a surgical condition, as is also a clinic upon specific urethritis by Dr. B. C. Corbus. The relationship of oral foci of infection to systemic disease is refreshingly presented by Dr. H. H. Schuhmann, who, though a Chicagoan, is not convinced of the correctness of Rosenow's findings. Dr. Frank Smithies covers the diagnostic features of retroperitoneal sarcomata, and the number concludes with a consideration of constipation by Dr. Joseph C. Friedman.   T. G. M.

PULMONARY TUBERCULOSIS: ITS DIAGNOSIS, PREVENTION, AND TREATMENT. By W. M. CROFTON, M.D., Lecturer in Special Pathology, University College, Dublin, etc. Pp. 122; 20 illustrations. Philadelphia: P. Blakiston's Son & Co., 1917.

THIS little volume on pulmonary tuberculosis deals with bacteriology, anatomy, histology, physiology, methods of infection,

pathology, diagnosis, prophylaxis, treatment, and the manufacture of vaccines. If one grants there is a need for so small a sketch of so large a subject he at least wonders why some topics like diagnosis receive rather scant attention and others, like vaccines, attract a considerable amount of consideration. The discussion of unsettled questions also occupies a relatively large space. At the same time the author has included a good deal of valuable material. Emphasis is laid on the part secondary organisms play in producing symptoms and on the value of treating these invaders with vaccines. Regarding prophylaxis against tuberculosis, the author says: "Everyone gets the infection. Since this is so it seems an almost hopeless task to try and cut off the source of infection, and we must therefore place our reliance on the individual resistance," and preventive measures other than increasing individual resistance are disregarded. The reasons for employing iodoform therapeutically are not convincing, but the author enthusiastically recommends its use. The experience of the author with therapeutic pneumothorax in suitable hemorrhage cases corroborates the results of many others. Mention is made of two cases of hemoptysis developing anaphylaxis following the injection of normal horse serum given by the intravenous route.   C. M. M.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Examination of a Regiment Infected with Bacillus Paratyphosus A, with Special Reference to Normal Carriers.—The occurrence of Bacillus paratyphosus A in the stools of men exposed to infection with this organism is reported by KRUMWIEDE (*Jour. Infect. Dis.*, 1917, xxi, 141), who examined the stools of 843 men of the 14th Infantry, New York N. G., after their return from the Mexican border. This regiment had been badly infected with Bacillus paratyphosus A, about 215 cases of paratyphoid infection having been diagnosed among 1000 men. Fifty-seven cases of the disease were included in this number, and among them the percentage of positive findings in the stools was much greater during the first week of the disease than in typhoid fever, being 83 per cent. In the second week 50 per cent. of the cases showed bacilli in the stools, and in the third and fourth weeks the percentage fell, unlike typhoid, in which the percentage of positive findings increases from the first week, reaching the maximum during the third week. Excluding these 57 cases there were 786 men examined, of whom 32 or 4 per cent., gave positive fecal results. None of these men gave any history of illness previous to or succeeding the examination. These histories were in all probability reliable, so that the positive cases should be considered normal carriers, that is, men who without suffering the disease, harbor and excrete the bacilli usually for a short length of time. The percentage of carriers (4 per cent.) is very high, but probably explainable by the high degree of exposure to infection. The authors used in the examination of the stools a brilliant green agar previously reported (*Jour. Infect. Dis.*, 1916, xviii, 1), and comparative results with Endo plates were greatly in favor of the brilliant green agar, the Endo plates giving only 52 per cent. of the total positives obtained upon the dye agar.

SURGERY

UNDER THE CHARGE OF

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Treatment of Recent Gunshot Wounds with Bismuth-Iodin-Paraffin Paste.—COLLEDGE and HAMMOND (*Lancet*, July 14, 1917, p. 49) say that a large number of cases have now been reported in which the bismuth-iodin-paraffin paste (B. I. P. P.) has been employed, with satisfactory results, in cases suppurating freely. The writers wish to record their experience in recent wounds as encountered in a casualty clearing station and to advocate its use in recently infected wounds in which suppuration has not yet been established. The method rightly used has the following advantages: The wound can be closed by sutures, rendering prolonged drainage unnecessary, and in the great majority of cases there is no suppuration. No change of dressing is required and much disturbance of the patient is avoided—a most important matter to freshly wounded men to whom rest is essential. It greatly increases the facility and reduces the discomfort of transport, apart from wounds of the viscera and central nervous system, the management of compound fractures presents the most difficult problem for the surgeon in a casualty clearing station, and it is in this class of cases that the writers have found the method particularly valuable. The technic is described as follows: The patients usually arrive in a filthy condition, encrusted with mud. The skin around the wounds, for now they are usually multiple shell, bomb, or grenade wounds, is cleaned with ether soap and rendered as surgically clean as possible. The part is surrounded with dry sterile towels. Surrounding the entry and exit wounds there is always a margin of necrotic skin heavily infected with microörganisms. This is removed by excising a ring of skin one-eighth of an inch wide. The wound is then freely opened up and all foreign bodies and loose pieces of bone are so far as possible removed. Further, all devitalized muscle is resected and bleeding-points secured. This resection extends not only to muscle, which is obviously necrotic, but also to areas which are devascularized and non-contractile. It is in muscle in this condition that gas gangrene begins to spread. Although this procedure is most important, the writers have had long enough experience to know that in itself it is insufficient to prevent the subsequent development of obvious signs of infection in compound fractures. The raw surface is then well swabbed with methylated spirit, and the B. I. P. P., consisting of 2 parts of iodoform to 1 of bismuth subnitrate, with sufficient liquid paraffin to produce the consistency of Devonshire cream, is smeared all over the wound and the ends of bone with a piece of dry gauze. It should be well rubbed in to form a thin film on the surface, and care should be taken not to leave any excess. It is convenient to leave the ligaturing of bleeding-points until this stage, as otherwise the ligatures

are apt to be rubbed off. Gaps in muscle can be brought together by catgut stitches when necessary. The wound is then sewn up with interrupted fishgut sutures and a dressing of dry sterilized gauze is applied; this is covered with wool, and, if required, a splint is applied. In favorable cases the dressings need not be disturbed until the patients are evacuated to the base, as it is an invariable rule to examine the wound before the patient leaves. If the outer dressing becomes stained with discharge it should be changed without disturbing the gauze in contact with the wound. If the patient has to be evacuated immediately to the base it is advisable to insert the fishgut stitches, but to leave them untied or only loosely tied. They can then be tightened later on without fear of tension being caused in the wound by retained discharge. This applies particularly to very extensive wounds. The writers conclude: The method is applicable to recent as well as to wounds several days old. There is no increased liability to gas gangrene if care be taken to eliminate that danger by free incision of damaged tissue. It is the simplest and most reliable method the writers have had the opportunity of employing of avoiding suppuration in infected gunshot wounds. It contributes greatly to the comfort of the patients for the following reasons: wet dressings and irrigations are avoided; and as the dressings need seldom be changed there is a minimum disturbance of the injured part.

Laceration of the Inferior Cava Repaired by Suture; Recovery.— Cole (*Ann. Surg.*, 1917, lxvi, 43) says that an investigation of the literature shows very few instances of extensive lacertion of the inferior cava with recovery. While separating dense adhesions from a rapidly growing tumor in the upper right quadrant of the abdomen, two longitudinal rents were made in the anterior surface of the inferior cava, one about 3.5 cms., and the other about 1 cm. in length. A very profuse hemorrhage was controlled temporarily by a gauze pack. The first efforts to disclose the nature of the hemorrhage were unsuccessful. The pack was finally held firmly compressed by the assistant's hand, and the tumor rapidly removed as the patient was almost exsanguinated. The vena cava was finally exposed sufficiently to allow an ordinary serrated Pean type clamp to be placed upon the vena cava below the rent, a gauze sponge on a sponge holder controlling some slight oozing from above. Both lacerations were quickly whipped over with a single stitch of fine catgut on a fine needle. Upon removing the clamp and sponge there was very little oozing. The entire cavity was rather loosely packed with iodoform gauze and the retroperitoneal edges were stitched to the anterior peritoneal wall. The patient was pulseless at the end of the operation, but was carried through a quite exciting twenty-four hours with intravenous saline, and was discharged from the hospital within three weeks with the abdominal wound practically healed. Ten days after the operation the patient developed a quite extensive edema of his entire right leg. This persisted for several days but gradually disappeared by the tenth day. Two months after operation the patient had had no further complication.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

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SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

The Treatment of Pernicious Anemia.—LARRABEE (*Boston Med. and Surg. Jour.*, 1917, clxxvi, 553) says that it is still unfortunately true that we do not know the cause of pernicious anemia and that we must still regard it as invariably fatal. Much has been learned concerning its pathogenesis. The systematic treatment of pernicious anemia, in the opinion of the author, should be based upon the following plan:· Every case should receive arsenic, best administered continuously by mouth. If the Wassermann reaction is positive or if there is other evidence of syphilis, salvarsan should be used. Iron should seldom be given except during recovery from relapses, where the increase in red blood cells outstrips the increase in hemoglobin and the blood picture approaches that of benign anemia. The diet should always be carefully regulated with a view of controlling protein putrefaction and intestinal indigestion and preserving the nutrition. Hydrochloric acid and other aids to gastric digestion should be used freely. When the anemia is rapidly increasing, the careful use of catharsis and regular and thorough lavage of the colon and perhaps also of the stomach is in order. If the anemia still progresses and especially in hemorrhagic and aplastic states, transfusion should be done. If one or more transfusions are not followed by remission it is justifiable to remove the spleen.

The Effect of Extensive Venesection and Transfusion on Kidney Lesions in Severe Acute Mercuric Chloride Poisoning.—BURMEISTER (*Jour. Lab. and Clin. Med.*, 1917, ii, 500) found that copious venesection followed by transfusion of normal blood inhibits both qualitatively and quantitatively the characteristic degeneration usually found in the epithelium of the ascending loop of Henle in the kidneys of dogs acutely poisoned by mercuric chloride. He believes, therefore, that in desperate and other cases of acute mercurial poisoning, venesection followed by transfusion should be practised in addition to other therapeutic measures now in use.

Calcium Sulphide as the Chemical and Clinical Antidote for Mercuric Chloride Poisoning.—WILMS (*Jour. Lab. and Clin. Med.*, 1917, ii, 445) says that in advanced cases of mercuric chloride poisoning the intravenous method of injecting calcium chloride solution, grain for grain of the bichloride of mercury taken, is the safest and most rapid. An advantage of the intravenous method lies in the assurance that the patient receives the required amount of the antidote, and that it is more direct. Calcium sulphide may also be administered by mouth when

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the intravenous method is not practicable. When the discomfort or the condition of the patient warrants it, both methods may be used. The use of calcium sulphide by mouth may be continued until all symptoms of mercurialism have disappeared, since it is non-toxic. Recovery has taken place, when the antidote was administered by mouth, as late as twelve hours after taking 7.5 grains of bichloride of mercury, and thirty hours when administered intravenously. The calcium sulphide solution must be freshly prepared for intravenous use or it loses its sulphur and becomes ineffective. Calcium sulphide solution should not be used stronger that 1 grain to 1 ounce of water. The solution should be boiled and filtered through cotton. The calcium sulphide solution, if deteriorated, will produce severe convulsions, owing to the free action of the calcium on the spinal cord, hence the necessity of a fresh solution. When calcium sulphide is to be given by mouth it should be administered, in the tablet or crude drug form, 2 to 5 grains every hour, until an excessive amount is taken. The author believes that local antidotes in the stomach in the form of the whites of eggs and lavage with large quantities of water is useless; bichloride of mercury is so quickly absorbed from the stomach that very little remains in the stomach unabsorbed at the end of five minutes. The vomiting by this time is so profuse that if any free bichloride of mercury were still present in the stomach it would not remain long enough to cause further damage. Wilms believes that calcium sulphide is the quickest, simplest and surest antidote for mercurial poisoning at the present time. He cites experimental and clinical evidence to warrant this belief.

The Neutralization of Virus of Poliomyelitis by Nasal Washings.— Amoss and Taylor (*Jour Exper. Med.*, 1917, xxv, 507) in a series of 56 experiments found that washings of the nasal and pharyngeal mucosæ possess definite power to inactivate or neutralize the active virus of poliomyelitis. This power is not absolutely fixed, but is subject to fluctuation in a given person. Apparently inflammatory conditions of the upper air passages tend to remove or diminish the power of neutralization. But irregularities have been noted, even in the absence of these conditions. The neutralizing substance is water soluble and appears not to be inorganic, it appears to be more or less thermolabile, and its action does not depend on the presence of mucin as such. It is suggested that the production of healthy carriers through contamination with the virus of poliomyelitis may be determined by the presence or absence of this inactivating or neutralizing property in the secretions. Whether this effect operates to prevent actual invasion of the virus and production of infection can only be conjectured. Probably the property is merely accessory and not the essential element on which defence against infection rests.

Pertussis Vaccine—Its Value as a Curative and Prophylactic Agent in Whooping-cough.—Luttinger (*Jour. Am. Med. Assn.*, 1917, lxviii, 1461) believes that the results obtained at the whooping-cough clinic and by over 180 private physicians and health officers warrants the routine administration of pertussis vaccine for both curative and prophylactic purposes. The best time to institute the vaccine treat-

ment, except as a prophylactic, is the first and second week of the paroxysmal stage. When the proper vaccine is given and the method of the New York Health Department is employed, the disease is materially reduced in duration and severity. The presence of subconjunctival hemorrhages in prophylactic cases which were protected by the vaccine seems to point to its specific immunizing action against the paroxysms and to the fallacy of the hitherto accepted theory that these hemorrhages are due to the violence of the cough.

PEDIATRICS

UNDER THE CHARGE OF

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Observations on the Presence of Bacillus Abortus Bovinus in Certified Milk (Preliminary Notes).—FLEISCHNER and MEYER (*Am. Jour. Dis. Children.*, September, 1917, xiv, No. 3). Many workers have tried to show by experimental studies that raw milk is never a safe milk and that pasteurization is the only safe precaution. Some States have passed legislation requiring the pasteurization of all milk except certified milk. Some observers have shown that certified milk is not safe without pasteurization. The authors of this paper feel that in addition to the ordinary tests made by certifying commissions, specimens should be injected into guinea-pigs in order to observe whether or not tubercular lesions are produced. There is nothing in the literature in regard to such tests having been made with certified milk. The authors collected samples of certified milk from regular distributors and injected guinea-pigs with the specimens. Acid-fast bacilli were found in the spleens, lymph nodes, and sex organs. These were the Bacillus abortus bovinus. As a result of their work, and from a *résumé* of the literature, the authors express themselves as follows: "So far as can be concluded in a preliminary report from a limited amount of material it may be said: (1) Bacillus abortus is, for practical purposes, always present in the certified milk produced in the San Francisco Bay regions. (2) Tubercle bacilli are not present in this same milk in sufficient number to give tuberculosis to guinea-pigs, although this conclusion may prove incorrect on further experimentation. (3) If the above conclusion is correct there is no necessity for pasteurizing certified milk on account of any danger that it may possess as a disseminator of bovine tuberculosis to infants. (4) It is not unlikely that in many previous milk tests for tubercle bacilli the anatomical lesion of bovine abortion disease in the guinea-pig were mistaken for tuberculosis. (5) If the Bacillus abortus is present in certified milk to the extent evident from these experiments it is difficult to consider it pathogenic for infants without it, so far as it is known, ever having produced recognizable lesions on postmortem examination. (6) The result of this work, however, is one more definite indication that it is

of the greatest importance that the abortus problem should be considered from every angle to be absolutely certain of its bearing on the health of infants."

Aural Complications of the Exanthemata.—LYNAH (*Arch. Pediat.*, August, 1917, xxxiv, No. 8). The percentage of acute suppurative otitis media in the exanthemata is governed by the degree of severity and the duration of the nasopharyngeal lesion at the onset of the disease. In diphtheria the percentage of ear infections varies from 2 to 4 per cent., the greatest number being in the intubated cases. In intubated cases fed gavage 6 to 10 per cent. developed ear complications. In scarlet fever the percentage is seldom below 10 per cent., and is sometimes as high as 30 per cent. Most aural complications occur early during the first to the third week, but they may occur as late as the tenth week after scarlet fever. The author thinks that the local nasopharyngeal lesion was wholly responsible for all of the otitic complications. In measles the percentage of aural complications varies with the severity of the infection from 10 to 12 per cent., but may be as high as 20 per cent. Most of the infections develop in the catarrhal and postcatarrhal stages, and seldom later than the second week. Sometimes the ear complications in measles are extremely violent, and the writer of this paper has seen a case in which middle ear and mastoid disease developed on the fifth day and acute purulent labyrinthitis developed on the eighth day, the patient dying two days later. "Pain was frequently masked at the onset, and as a constant sign was rather unreliable; hardness of hearing might make its appearance early and always called for prompt aural examination. The temperature was invariably high at the onset in all severe cases of scarlet fever and measles, and the otitic complications seemed to have no more influence on the temperature curve than the necrotic throat lesion or cervical glands. In many instances subperiosteal abscesses might develop with no rise in temperature, and it was not infrequent in scarlet fever and measles to find extensive destruction of the mastoid process and the temperature not be elevated over 99°. The temperature curve, while usually an important symptom, was frequently subject to wide variation." Such complications as brain abscess, sinus thrombosis and the like were rare. Surgical treatment is recommended. Free incision of the drum is preferable to spontaneous rupture. In complicated cases surgical results were not gratifying. "In all cases of exanthemata the aural condition should be carefully followed from day to day, or else aural complications might be far advanced before the condition is recognized."

Phenolsulphonephthalein Elimination in Infants and Young Children.—GITTINGS and MITCHELL (*Am. Jour. Dis. Children*, September, 1917, xiv, No. 3). This paper is based on a study of 75 cases. Males were used in order to facilitate the collection of the urine. The ages varied from three weeks to ten years. The technic differed somewhat from the usual technic followed for adults. No preliminary catheterization was performed, but the older children voided before the test. The infants and younger children were placed on Bradford frames with a clean pad of cotton under them. If any urine was lost during the test the results were discarded. 0.5 c.c. of a solution containing 3 mgs. of

phenolsulphonephthalein (half the adult dose) was injected deeply into the lumbar muscles. Catheterization at 70 to 120 minutes or both was performed except in the older children who could void. The specimens were alkalinized and diluted to 500 c.c. instead of to 1000 c.c. to allow for the half-dose administered. As a result of these tests the following conclusions were reached: "(1) The observation is confirmed that the elimination of phenolsulphonephthalein is not markedly decreased in any disease other than renal. (2) Even the youngest infants and children show about the same capacity for phthalein elimination as do adults. (3) Preliminary catheterization in the absence of retention of urine is unnecessary. (4) For purposes of comparison a uniform technic should be adopted and maintained. (5) We believe that in children a single collection exactly two hours after the injection into the lumbar muscles of 6 mgs. of phthalein should be the method of choice. The necessity for continuous or repeated catheterization would thereby be avoided. (6) An entirely different standard must be used for the accelerated output resulting from the intravenous injections. The latter need only be employed when local conditions, such as marked edema, prevent the use of the intramuscular route."

OBSTETRICS

UNDER THE CHARGE OF

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Death during the Puerperal Period from Rupture of the Bladder.— HUXLEY (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) reports the case of a primipara, whose fetus was in the right occipito-posterior position, who was delivered by her physician by forceps. The physician instructed the nurse to catheterize the patient, but this was not done, as it was thought that the bladder was emptied spontaneously; there was a tear in the perineum which was closed. Eight days after the birth of the child, after a sudden stretching movement of the right arm, the patient was seized with violent abdominal pain, collapse, and vomiting. On admission to hospital the patient was in shock; the abdomen greatly distended, but not very rigid nor very tender. There was dulness over the pubes and evidently free fluid was in the abdomen. The patient stated that no urine had been passed for about thirty days and by the catheter about 40 ounces of somewhat offensive urine was removed. On the following morning 35 ounces were taken. Ten days after confinement the patent died. At autopsy between 2 and 3 pints of turbid urine was in the abdominal cavity and there was a free peritoneal exudate. The bladder was adhesive to the anterior abdominal wall and the posterior part adhesive lightly to the anterior surface of the uterus. The wall of the bladder was very thin, as if it had been overdistended. At the summit of the bladder fundus was a tear two and a half inches in length through which urine had

escaped. This case raises the interesting question "when and why rupture of the bladder occurred." It seems most probable that the sudden stretching movement which the patient made on the ninth day of the puerperal period and which was followed by acute pain was the active cause of the bladder rupture. In accounting for this accident it is remembered that forceps was applied to the fetal head when the bladder was distended. This produced increased pressure. The fact that the bladder had been distended had produced atony and the sudden reaching movement which the patient made had caused a strong and sudden contraction to the abdominal muscles sufficient to empty the bladder. One similar case is found reported by GENTILES (*Brit. Med. Jour.*, 1883, i, No. 3). The patient was a multipara and had suffered from retention of urine. She had an abortion at three months and developed acute abdominal symptoms, resulting in death thirty hours after. At abortion rupture was present and was thought to have resulted from expulsive labor pains acting upon the distended bladder.

Ovarian Cyst Obstructing Labor.—SALISBURY (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) adds to the literature of this subject three cases. In the first the patient had been in labor six days at full term, and having strong uterine contractions. The child was dead and the head fixed in the pelvic brim in the right occipitoposterior position. There was complete dilatation and a large tense cyst filled Douglas's pouch below the presenting part. When the abdomen was opened and the uterus lifted out, a dermoid of the left ovary was withdrawn and ruptured. The cyst was removed, the uterus replaced, and the fetal head pushed into the pelvic brim. The patient was placed in the lithotomy position, the occiput manually rotated to the front, and with axis-traction forceps a large, dead child was delivered. The abdominal wound was closed, the patient making a good recovery. This is thought to have been a safer method than delivery by Cesarean section. In the second case, under the care of a midwife, a mass was felt behind the vagina above which was the fetal head. Under very strong pains a living child was born and the mass disappeared. The patient vomited once but seemed fairly well. She was admitted to hospital and the abdomen opened when a tumor of the left ovary weighing $2\frac{1}{2}$ pounds was found to have ruptured. There was a quantity of blood, serum, and mucoid material in the peritoneal cavity. The cyst and fluid were removed, a tube used for drainage, and the patient recovered. The third case was sent to hospital in labor because the doctor had found two polypi in the vagina. The patient was at full time in her third pregnancy. On admission she was having pains, the child living, and presenting as a first vertex. By palpation a small cyst of the left ovary was found on the left side. In Douglas's pouch there was a very hard, angular mass continuous with a softer mass on the left side of the pelvis. The patient's labor pains subsided, although amniotic liquid escaped before the abdomen was opened. As it was impossible to reach the tumors, the uterus was first emptied by section and a living child delivered. The pelvic mass was a dermoid of the right ovary as large as a cocoanut which contained a mass of bone and three teeth. There was also a dermoid of the left ovary above the pelvic brim. Both tumors were removed, the patient making an uninterrupted recovery.

Modern Practice in the Induction of Labor for Contracted Pelvis.—
GUICCIARDI, in the clinic at Venice (*Annali di Ostetricia*, 1916, Nos. 1
and 2) has employed various modern methods in dealing with contracted
pelvis. As the result of his clinical experience he has greatly limited
the induction of labor. Before proceeding to induce labor, he would
have the pelvis examined by the roentgen rays, and would choose a
time not earlier than the thirty-fifth or thirty-sixth week. He would
also not induce labor in any case where the pelvis was highly contracted.
Every effort should be made in inducing labor to secure the spontaneous
birth of the fetus; fetal mortality increases in direct proportion, as
labor must be terminated by obstetric operations. Care must also
be taken that in the endeavor to stimulate labor, voluntary uterine
contractions may be set up which may destroy the fetus through press-
ure. In the use of forceps it is very essential that complete dilatation
of the cervix and lower portion of the uterus be present. Otherwise
the mother will be injured and the child also subject to severe pressure.
Artificial dilatation with elastic bags should be practised if necessary
before the application of forceps. Where great difficulty is found in
securing proper dilatation it may be necessary to abandon delivery
through the vagina. Where the head does not enter the pelvis the use
of forceps is contra-indicated. Complications in labor which directly
threaten the fetus, such as prolapse of the cord or the development
of an unfavorable presentation and position, call for an abdominal
delivery. Embryotomy upon the living fetus should be declined, and
especially dangerous are violent and fruitless efforts at delivery made
by unskilful persons. In highly septic cases with foul and putrid dis-
charge, embryotomy may be more dangerous than extirpation of
the uterus. The classic Cesarean section remains the method of choice
with the highly deformed pelvis. Its sphere of application is steadily
widening. Complications in section may arise from previous infec-
tion, from imperfect or infected suture material, from paralysis of the
placental site, or other abnormal conditions affecting the uterus. In
a certain number of cases sterilization must accompany the perform-
ance of section. Here the question as to whether the parents have
children already must be taken into account; also the facilities which
will be available in caring for a premature child. While pubiotomy
will occasionally give a good result, its performance is frequently accom-
panied by complications, and under certain conditions it does not give
a satisfactory solution of the problem. In cases in which pelvic con-
traction is but slight, it seems as if delivery through the vagina might
easily be possible; the test of labor may be awaited. Should this fail,
one has the choice between the classic Cesarean section and the supra-
symphyseal method. Latzko's operation frequently gives results.
In the severely septic cases it may be more prudent to do embryotomy
in the interests of the mother rather than risk any form of major
operation. In comparing the various methods of section the possi-
bilities of repeated section must be taken into account. In choosing
a method of delivery in contracted pelvis, the interests of mother and
child, the condition of the family, and the possibilities for proper
care for the infant must all be taken into consideration.

GYNECOLOGY

UNDER THE CHARGE OF

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Division of Ureter in Pelvic Operations.—When a ureter has been accidentally cut in the course of a pelvic operation, the surgeon usually has a choice of several procedures in considering the best method of repairing the damage. According to Graves (*Boston Med. and Surg. Jour.*, 1917, clxxvi, 149) ligating the ureter has certain advantages over anastomosis and implantation. It requires very little expenditure of time, usually an important consideration, as the operations in which the ureter is cut are generally of great severity. If the end of the ureter is properly tied, there is little danger of leakage and fistula. Hydronephrosis will occur in 80 per cent. of cases but it is not great and gradually subsides as the kidney atrophies. If a dangerous hydronephrosis should occur, the kidney may be removed at a later operation. Anuria appears in about 1.6 per cent. of cases after ligation of one ureter. It is highly probable that ureteral anastomosis is more commonly followed by fistula formation and infection than is the ligature operation. Furthermore, it is evident from the literature that most of the cases of death following ligature of the ureter have been due to shock following some extremely severe operation rather than to the closure of the ureter. Graves prefers an anastomosis to an implantation, since by the former only one organ is injured, and if a fistula or pyelonephritis ensues, the kidney may be removed and the trouble cured by one operation. On the other hand, if a fistula follows implantation of the ureter into the bladder, the surgeon then has to deal with two injured organs. The operation for reimplantation or closure of a uretero-vesical fistula is, in Graves's opinion, less satisfactory than a simple nephrectomy, such as might be necessitated by trouble from ligature or anastomosis. If implantation is imperative, as might be the case in the presence of injury of the other ureter, or a functional deficiency or disease of the opposite kidney, the location of choice for implantation would be, of course, in the bladder, if the proximal end of the ureter is sufficiently long. In case of emergency the ureter may be left to drain from the vagina or carried out through the skin. Implantation into the intestine is not desirable on account of the almost inevitable ascending infection of the kidney. Implantation into the appendix or of one ureter into the other or even into the Fallopian tube are operations that have been advocated from experiments on animals and on the cadaver but probably have no practical value.

Treatment of Ectopic Gestation.—Contrary to the views of many, immediate deaths as a result of hemorrhage in cases of ectopic pregnancy were rare in Werder's experience (*West Virginia Med. Jour.*, 1917, xi, 233) in a series of over 200 cases. There is a strong tendency in most cases for the bleeding to become checked spontaneously, especially under proper treatment, but persistent watching is required on

account of the constant danger of recurring hemorrhage. Shock is often an important factor, the elimination of which should be undertaken before operation when possible, thereby reducing the operative risk. Delay of operation is therefore generally advisable in grave cases after rupture, particularly when bleeding seems to be at least under temporary control. This will enable us to overcome the attending shock and also to gain the additional advantage of an improved circulation through the refilling of the depleted bloodvessels, advantages which will greatly minimize the risks attending the operative treatment.

The treatment of that rare but interesting form of extra-uterine pregnancy in which fetal life escapes destruction at the time the tragic symptoms occur, and continues to develop until the fetus has reached a viable age, presents some interesting features. The greatest difficulty and source of danger in this condition is the placenta, since the hemorrhage encountered in the removal of the living placenta is truly frightful and frequently fatal. Nevertheless, Werder believes that the only rational treatment is the entire removal of the placenta and sac, which can be done without undue hemorrhage if the uterine and ovarian arteries are controlled before the removal is begun. When these arteries are not accessible we may resort to compression of the abdominal aorta, by which means we can temporarily, at least, control hemorrhage until the placenta is out of the way and its principal blood supply is secured.

After-results of the Interposition Operation.—AYRES (*Am. Jour. Obst.*, 1917, lxxvi, 451) has had the opportunity of examining 37 patients upon whom the interposition operation had been performed, the examination including a cystoscopic study as well as a vaginal examination in nearly every case. Of the entire series, only 16 patients were free from some undesirable symptom, although in many cases the trouble was insignificant. An analysis of the 21 cases that presented undesirable symptoms shows that cystitis was complained of in 9 cases, prolapse of the fundus in 4 cases, recurrence of the cystocele in 2 cases, incontinence in 3 cases, persistent bleeding in 2 cases and separation of the anterior vaginal wall in 1 case. Considered from an anatomical result the appearances are better, since 30 of the 37 patients could be said to have a perfect cure of cystocele, rectocele and prolapse. One very significant fact is that out of the total of 21 unfavorable cases, 11 occurred in patients operated upon for complete prolapse. Out of the 9 cases of cystitis, 5 occurred in such individuals, while all the cases that had poor anatomical results occurred in those operated upon for complete prolapse. Ayres has analyzed the results in this series and has drawn certain conclusions in regard to the indications for the interposition operation. Obviously it is an unwise procedure during the child-bearing age and likewise is contra-indicated in cases of prolapse of the third degree, but may be used to advantage in the lesser degrees of prolapse with cystocele. When fibroids are present or a condition of fibrosis is suspected, denoted by profuse, irregular bleeding, hysterectomy should be performed and the other indications met. When the operation is indicated, large uteri should be reduced in size in the course of the operation and an effort be made to keep the bladder floor level; furthermore, one should not hope to cure incontinence without strengthening the sphincter of the bladder.

OTOLOGY

UNDER THE CHARGE OF

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The Effects of High Explosives on the Ear.—WILSON (*Jour. Am. Med. Assn.*, June, 1917). The majority of the two hundred patients exhibiting nerve symptoms were examined by the author at periods varying from within twenty-four hours to one week after the injury, and of this number 50 complained of deafness in varying degree. Seventeen of the 50 cases gave evidence of injury to the internal ear as the result of the explosion. In the remainder the deafness in many instances had been merely temporary and there had been no disturbance of equilibrium in the cases of persistent impairment of hearing. This was found to be due in some to extralabyrinthine causes, the result of an old middle-ear suppuration or an occlusion of the external canal. Of the 17 cases, 6 had definite middle-ear trouble before the concussion; of the remaining 11 with no previous history of ear trouble, 6 had evidences of a recent perforation of the drum-head and 12 complained of vertigo and gave demonstrable signs of disturbance of equilibration. In regard to the character of the injury in these cases and the treatment to be employed, the author concurs in the general opinions deduced from the existing imperative opportunity for observation, and emphasizes the importance of complete rest and recumbency for a period of at least ten days after the injury and that more immediate removal to a base hospital is liable to retard recovery by the injurious effects incident to transportation.

War Injuries and Neuroses of Otological Interest. Concussion Deafness.—MARRIAGE (*Jour. of Laryngol., Rhinol. and Otol.*, London, June, 1917). These cases the author divides into two etiological classes: those the result of continued explosion of guns firing day after day, and those consequent upon the bursting of a shell fitted with high explosive in the immediate vicinity of the patient. The former belong usually in the class of results similar to those observed in foundrymen, machinists, boiler-makers and civilians engaged in corresponding occupations and there is, usually, persistent deafness in a moderate degree if the soldiers have been long exposed. The deafness due to shell explosion is generally very extreme for a short time and is sometimes accompanied by unconsciousness. In one instance the author saw a shell burst just behind a lieutenant without wounding him, but rendering him completely unconscious for an hour. When he recovered consciousness he noted marked deafness in both ears and intense headache, but no subjective noises, and no vertigo, nor was there, either at the time or later, hemorrhage or discharge from the ears. Four days later he heard the spoken voice two feet away from each ear but high tones, as represented by a loud ticking watch, of three and a half or four feet

normal distance; not at all with the tuning-fork; both air and bone conduction were much subnormal, the former, however, being better than the latter; both drum-heads were practically normal; eighteen days after the explosion the hearing had become normal. The treatment adopted by the author in these cases is rest in bed, bromides in the early stages and later strychnin. In the matter of prognosis, time is the best consultant; if marked improvement has not been made within six to eight weeks the prognosis is bad, and even when the hearing returns subjective noises often persist. In default of an opportunity for postmortem examination in any of his cases the author infers that the seat of the concussion injury is chiefly peripheral as in the cases under his observation. The deafness was rarely associated with rupture of the drum-head, which is in accordance with the generally accepted view that rupture of the drum-head lessens the concussion effect in the middle ear; in very severe concussions the author suggests the possibility of concomitant central injury, such as hemorrhages into the pons, medulla or cerebellum. Psychical deafness as the result of shell shock is usually binaural and occurs usually in cases in which the shock has been especially severe as, for instance, being buried by a shell without visible evidence of injury. The deafness is usually absolute, there being no hearing either by air or bone conduction and it is usually accompanied by other nervous signs and symptoms, loss of voice, narrowing of the field of vision, tremors, irregular paralyses and areas of anesthesia; spontaneous nystagmus is absent. The author agrees with Milligan and Westmacott that in these cases there is a temporary suspension of neuron impulses from the higher cortical cells of the central nervous system to the periphery, their view being that the hiatus or synapse interfering with the flow of nervous stimuli is a central and not a peripheral one, for the reason that in so many of the cases of sudden blindness and sudden deafness no trace of any organic lesion, peripherally, was to be found and, moreover, the rapid recovery of a large proportion of the patients was a strong argument in favor of the supposition that none had occurred. Mr. A. Cheatte is quoted by the author as reporting 2 confirmatory cases, 1 that of a private who, during a bombardment suddenly became unconscious without any definite assignable cause and so remained for two days and on recovering consciousness was found to be completely binaurally deaf, without vertigo, and without objective evidence of an aural lesion, but for the period mentioned he could not hear the loudest shouting or even his own voice. The vestibular reaction to cold was normal. The second case was that of a Belgian soldier blown from his bicycle in the retreat from Antwerp and completely deaf in both ears, aphoric and paralyzed in his left arm and leg from that time up to July, 1916; in this case rapid recovery ensued upon electrical applications, previous forms of treatment, including hypnosis having failed. The difficulty of distinguishing this form of deafness from malingering is often great but can generally be accomplished by a thorough examination of the malingerer, who is usually sullen and defiant and fully conscious, being at some time during the tests revealed in his true character while the patient with psychical deafness has the signs and symptoms of a nervous breakdown. Among the experiences of other observers the author reports some of especial interest. Two, for instance, which under different

causative conditions exhibited similar results. One seen by Mr. S. Hastings was wounded on the right cheek by a bomb; when examined eighteen days later the manubrial vessels were injected and the tympanic cavity evidently filled with blood, the Politzer acoumeter was heard at a distance of two inches, the Rinné test was negative and the bone conduction normal. Six days later bubbles were seen in the hemorrhagic contents of the tympanum and the hearing materially improved, while at the end of a fortnight later the fluid in the tympanum had disappeared, the drum-head was somewhat retracted and the hearing for the acoumeter was three feet. Mr. A. Cheatte also reports a case of hemorrhage into the middle ear due to a parachute descent, the airman, twenty-one years of age, having descended thirteen thousand feet in four minutes. The only ill effects of this rapid change of air-pressure were impairment of hearing, a feeling of fulness in the left ear and a sensation of crackling on yawning. The left middle ear was found to be filled with blood with an intact drum-head, the hearing was but slightly decreased. Nothing was done in the way of treatment and at the end of a month the blood had disappeared and the hearing became normal.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Cultivation and Immunological Reactions of the Globoid Bodies in Poliomyelitis.—Amoss (*Jour. Exper. Med.*, 1917, xxv, 545). The globoid bodies of Flexner and Noguchi have a definite relation to epidemic poliomyelitis. They have been found repeatedly in lesions in both man and monkey; they have not been seen in lesions or conditions other than poliomyelitis; they have produced experimental poliomyelitis in monkeys and have been recovered from lesions so produced. Like the Treponema pallidum, they are so parasitized that they are refractory to artificial cultivation. Subcultures, however, when once established grow with comparative ease, always remaining anërobic, but becoming saprophytic and non-pathogenic. The author reports two additional cultures of globoid bodies, obtained from the nervous tissues of monkeys in which experimental poliomyelitis was produced. A bit of fresh rabbit kidney is indispensable to the original cultivations. After the virus has become less parasitic it will grow, though less luxuriantly, in media containing boiled kidney and still less abundantly

in media without any fragment of the organ at all. No cultures multiply in broth even in the presence of the kidney fragment. Adapted cultures grow freely in monkey serum with kidney, less in horse and rabbit serum and least in human serum. Amoss injected rabbits and monkeys with globoid bodies in order to develop antisera which might show agglutination and complement-deviation, and tested the sera of human beings and monkeys which had recovered from poliomyelitis against cultures of globoid bodies. The rabbits responded slightly with the production of antibodies to the injection of cultures of globoid bodies; the monkeys under the same conditions responded only when the cultures were injected into the central nervous system. The response never led to more than slight reactions of agglutination and complement-deviation with the cultures. Monkey serum showed even less agglutination and no complement-deviation. Human serum gave no complement-deviation with antigen derived from globoid bodies. The maximum agglutinative and morphological changes produced in the globoid bodies cultivated in immune monkey serum were obtained in the first generation; after several subcultures in the immune serum, the reversion to normal took place in one generation in a non-immune serum.

Arthritis Deformans as an Infectious Disease.—There is still much controversy and lack of agreement in the clinical and pathological interpretation of the lesions in chronic articular diseases. Clinically, we have a number of classifications based upon the condition of the joints as found in life. The classifications take into account mainly the outstanding features which present themselves late in the disease. Thus, the terms hypertrophic and atrophic, as applied to the joint lesions indicate such distinctive types that they are very acceptable to the clinician. The nomenclature of joint diseases has become so deeply rooted that the impression is conveyed that each term used suggests a specific etiology. Because of the chronic course of these affections it has been impossible to study the cases and the individual lesions through the entire course of the disease. NATHAN (*Jour. Med. Res.*, 1917, xxxvi, 187) has undertaken a study of the pathological lesions in joints along with an experimental investigation of infectious inflammatory processes in the joints of animals. On a previous occasion he had accepted the common interpretation that the joint conditions were either of inflammatory origin or resulted from degeneration. Following upon his present study, he is more inclined to consider a similar mode of development in both. He has found that infectious agents are the most important factors in this disease, but he, furthermore, finds that the microörganisms present in different cases are not necessarily always the same. He has, furthermore, noted that both proliferative and degenerative phenomena occur in the joints of the same individual in polyarthritis as well as in cases of monarticular disease. He points out that the localization of the infection and the regions of greatest inflammatory reaction differ in the different cases. At times it is in the epiphysis, in the subperiosteum, in the capsule or in the surrounding loose tissues. Obviously, the localization of the infectious agent will lead to a different deformity. Pathological processes occurring beneath the joint cartilages may eventually lead to its atrophy or destruction.

By means of inoculation experiments, using the streptococcus, pneumococcus and staphylococcus, he repeated the work of Lexor. He was then able to produce arthritis in various grades of intensity. In his experimental work the acute non-suppurative lesions were readily obtained, but the animals were not permitted to survive sufficiently long periods of time to attain the chronic proliferative stages or the atrophic changes observed in man. He believes that it is not the specificity of the microörganism but its virulence, the resistance of the host and its location, which determine the variations of the morbid process. In man the local clinical phenomenon of the articular disease corresponds to the experimental arthritis in animals, including the decalcification and rarefaction of bone caused by the vascularization of the periosteum and marrow. He believes that it is fairly certain that the various forms of polyarthritis are caused by infection, and that, therefore, the classification of the so-called arthritis deformans into the infectious and metabolic types is no longer necessary so far as the joint diseases are concerned.

HYGIENE AND PUBLIC HEALTH

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Epidemiology of Pellagra in Nashville, Tennessee.—JOBLING and PETERSEN (*Jour. Infect. Dis.*, August, 1917) in a previous report (Ibid., 1916, xviii, 501) noted the epidemiology of pellagra based on a partial survey of the city of Nashville. In this report the physical aspects of the city, the relation of pellagra to the method of sewage disposal, the diet, as well as the evidence of the occurrence of contact in the development of new cases were fully entered into. The present paper concludes the field work connected with this survey which was amplified and completed during the summer of 1916. The authors conclude that so far as the epidemiology of pellagra is concerned, as studied under the conditions existing in Nashville, they cannot ignore the fact that the disease presents all the evidences of being in some way conveyed from one patient to another. It is practically a disease of the unsewered city areas, a family disease or almost as frequently a disease "of the house next door," and not only a family disease in the sense that the members live in the same house and eat the same food, but most frequently they found that relatives, not living under the same conditions, but frequently associating, have one after the other succumbed to the disease. The fact, too, that cases develop in houses adjoining pellagrins, previously emphasized in the report of the

Thompson-McFadden Commission, is of great importance, because the chances for the wider contact, "same block," to prevail are naturally much greater than for the lesser number dwelling in adjacent houses. The mode of occurrence of pellagra among the segregated negro colonies of the city is also of interest in this connection. To all intents and purposes the various groups live under identical economical conditions, and any variations in diet would be negligible. Pellagra occurs frequently in all except one of the groups. The only explanation possible is that there is little pellagrous contact for this group. The other negroes live surrounded on all sides by pellagrous whites; this particular group is, however, cut off from the adjacent white pellagrous population by a wide railroad trackage and on the other side is adjacent to a well-sewered non-pellagrous white zone.

Gas Production in Raw and Pasteurized Milk. — ALLEN (*Jour. Infect. Dis.*, August, 1917) states that pasteurization causes milk to become more favorable to the attack of the gas-forming colon bacillus and Bacillus aërogenes. These results seem to reinforce the impression long held by many milkmen that pure raw milk has a power of resisting changes which the same milk does not possess when pasteurized. Between raw and pasteurized milk there may be important differences, although chemical analyses may show no appreciable differences. In view of the fact that milk has its value strictly because of its relation to growth, in studying raw and heated milk, due consideration should be given to delicate biological tests which utilize growth as the means of producing comparative data. It should be more generally recognized that pasteurized milk, instead of receiving less care than raw milk, should receive greater care because of its lessened resistance to many detrimental changes which the appearance of the milk does not indicate. This is especially significant in that, in general, pasteurization has lengthened the period between production and consumption.

Studies of Bacillus Welchii, with Special Reference to Gas Gangrene. —SIMONDS (*Jour. Exper. Med.*, June 1, 1917, p. 819) states that gas gangrene develops much more frequently in wounds received on the battlefield than in those incident to accidents in civil life. This is probably due to differences in the character of the wounds in the two conditions rather than to differences in opportunity for infection with the group of organisms responsible for the disease. An examination of the uniforms of Belgian soldiers for spores of anaërobic bacteria of the group capable of causing gas gangrene showed that 90 per cent. of the uniforms of men from the trenches carried spores of organisms belonging to the group of B. welchii; and that the new uniforms as received by the Belgian soldiers, and the cloth from which these garments were made, contained spores of this group of organisms in the meshes of the goods in all samples examined. Material consisting of fragments of shells, bits of clothing and other débris, and pieces of lacerated tissues and blood clot removed from recent wounds (*i. e.*, two to eight hours old) of 20 soldiers was examined for the presence of organisms capable of causing gas gangrene. Of these, 15 contained either spores or vegetative forms of bacilli having the morphological and

biological characteristics of the group of B. welchii. Only 3 of these patients, *i. e.*, 20 per cent. of the positive cases, developed gas gangrene. In each instance the wound involved the large muscle masses of the thigh with much laceration of the tissues. The organisms reached the wounds in the form of spores only. It was only in the deep-lying injured muscle that conditions were favorable for germination of these spores and rapid multiplication of the bacilli, namely, anaërobiosis and a culture medium rich in fermentable carbohydrate (glycogen). In the pathogenesis of this infection in contaminated wounds, therefore, the lacerated muscle is the most important factor, and it is to this that attention should be directed in the prevention of the disease. After active growth in the dead muscle tissue has begun, it is probably the pressure of the gas developed from the glycogen that is responsible for the rapid dissemination of the organisms into adjacent healthy tissue. Because the presence of a fermentable carbohydrate is essential to the vigorous growth of B. welchii, and because cane-sugar has been used in the treatment of war wounds, 75 per cent. of which were found to be contaminated with spores of this group of organisms, it seemed desirable to study the effects of different concentrations of saccharose upon their growth. All of the ten strains studied multiplied rapidly and produced an abundance of gas in broth containing 5, 10, 20 and 40 per cent., respectively, of saccharose. In the 40 per cent. solutions the formation of gas was somewhat slower than in the lower concentrations. Only one strain produced gas, slowly, in 50 per cent. saccharose broth. None of the strains grew or produced gas in bouillon with 60 per cent. of cane-sugar. In the treatment of gas gangrene in the war zone, one of the most effective methods is the injection of pure oxygen gas into the affected and adjacent tissues. In order to investigate the mechanism by which pure oxygen in the tissues produced its apparent salutary effects, the gas was allowed to bubble for varying periods of time through tubes of anaërobic milk containing B. welchii. It was found (1) that different strains did not show the same resistance to the presence of oxygen; (2) that, after three hours' incubation, bubbling oxygen gas for twenty minutes through milk cultures did not appear to inhibit the growth in any way, for the tubes showed typical stormy fermentation after a further twenty-four hours in the incubator; (3) that bubbling oxygen for twenty minutes through less heavily inoculated tubes of milk caused death of the organisms in from four to twelve hours; (4) that bubbling the gas through such milk tubes for five to ten minutes did not destroy the bacteria, but either inhibited their growth or changed their ability to act upon lactose, so that there was only coagulation with little or no gas formation.

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THE BROADER ASPECTS OF HEMATOLOGICAL DIAGNOSIS.

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The morphological blood picture generally reflects certain
changes in the blood-forming organs, and all that a morphological
study really permits in the line of diagnosis. is a probable forecast
as to the nature of these changes. It is a fortunate coincidence in
some cases that the blood picture is sufficiently characteristic to
enable one to make a clinical diagnosis on the morphological appear-
ance alone. The extension of our knowledge along these lines has
brought to light many cases in which the application of the usual
criteria of blood examination has led to an erroneous diagnosis.
The tendency has been to rely too much upon the morphological
examination of the blood by an expert and to lose sight of the fact
that qualitative and quantitative changes in the morphology of
the blood are merely an index of more fundamental changes in the
blood-forming organs, and that these in turn are due to the pres-
ence of some underlying disease of either definite or obscure etiology.
With these reservations, and with similar reservations applied to
the bacteriological, serological, physical, and chemical examination
of the blood, there is probably no organ or system of organs or

structures which affords as many valuable diagnostic criteria as does the blood. The importance and utility of bacteriological and serological examinations need no further comment at this time. The development of accurate methods, especially as applied to small quantities of blood and the convenience of their application, has greatly increased the importance of the physical and chemical study of this fluid, and with the information thus obtained it has been found that the value of such examinations may be greater in some cases than the corresponding study of the excretions. Symptomatic conditions like hyperglycemia, acidosis, uremia, hydremia, etc., may be diagnosed with considerable rapidity and precision exclusively by an examination of the blood.[1][2] Inasmuch as each one of these conditions is usually associated with a corresponding clinical entity, a correct clinical diagnosis may often be made or confirmed by a properly conceived analysis of the blood alone.

A single morphological criterion rarely permits of as simple and clean-cut interpretation as a properly selected physical or chemical quantity. In morphological hematology it is necessary to work with the number and direction of groups of transitions in form and staining properties, and to correlate these changes with the qualitative and quantitative structural changes in the blood-forming organs. Therefore a clear understanding of the pathological morphology of the blood logically presupposes a knowledge of the histopathology of the blood-forming organs. The interpretation of the somewhat complex histopathology of the blood-forming organs may be greatly facilitated by a study of the fundamental phenomena of hematogenesis. It cannot be urged too strongly that prospective hematologists familiarize themselves first with the appearance of fetal blood and the blood formation in the liver and spleen of the human fetus before the bone marrow has appeared. The development and distribution of the lymph nodes in the human fetus at different ages is also worthy of careful study. In the following brief *résumé* of the histopathology of the blood-forming organs, certain arbitrary distinctions and restrictions are made solely in the interest of simplicity and uniformity in nomenclature without intentional prejudice to one or another of the so-called hematological schools or doctrines. In the examination of a large hematological material one will find that these distinctions and restrictions are not only justifiable but also decidedly useful.

Blood-forming tissue occurs in two essential types, lymphatic and myeloid. *Lymphatic tissue proper* is homogeneous and uniform in structure, and consists chiefly of small lymphoid cells identical

[1] Van Slyke, D.D., Stillman, E., and Cullen, G. E.: The Nature and Detection of Diabetic Acidosis, Proc. Soc. Exper. Biol. and Med., 1915, xii, 165.

[2] Butterfield, E. E., Erdwurm, F., and Braddock, W. H.: The Differentiation of Nephropathies, Cardiopathies, and Allied Conditions, AM. JOUR. MED. SC., 1916, cli, 63.

with the lymphocytes of the peripheral blood. The Malpighian corpuscles of the spleen and the follicles of the lymph nodes and of the intestinal lymphatic structures are prototypes of this tissue. In addition there are small, apparently isolated, groups of lymphoid cells scattered throughout the organs and tissues of the body. The *interfollicular tissue* is not classed with the lymphatic tissue proper on account of the absence or scarcity of small lymphocytes, the lack of homogeneity in structure, and its essentially different behavior under pathological conditions. The term lymphocyte is restricted to cells identical with the small lymphocyte of normal adult human blood. These restrictions are justified by the following facts: (1) in the majority of cases of lymphatic leukemia and lymphatic pseudoleukemia the newly formed tissue is remarkably simple and uniform in structure, and consists chiefly of cells which are identical in morphology with the lymphocytes of normal blood; germinal centers and large lymphocytes are absent; (2) in the development of the lymphatic structures in the human embryo neither germinal centers nor large lymphocytes are demonstrable; (3) there is no evidence of the regular participation of the germinal centers in the proliferation of lymphatic structures, nor is there sufficient evidence that the hypothetical large lymphocyte, supposedly identical with the cells of the germinal centers and the parent cell of both lymphocytes and myelocytes, is necessary for lymphocytogenesis. The identity of the cells of the germinal centers with the elusive large lymphocyte or with the lymphoblast is by no means proved, and the morphological characteristics claimed for the lymphoblast are neither sufficient to differentiate the lymphoblast from other cells, notably the undifferentiated cells of the myeloid group, nor to express the genetic relationship of the lymphoblast to the small lymphocyte.

Pale areas occurring in the lymph follicles in status lymphaticus and in local inflammatory conditions are often called germinal centers by the pathologist. These pale areas are loose in structure and often present signs of necrosis, while signs of active lymphocytogenesis are lacking. They are quite different from the germinal centers described by Flemming, and it is a question whether they are not regressive pathological structures due to local toxic effects or circulatory disturbances in the lymph node.

In contradistinction to the simplicity and uniformity of lymphatic tissue proper, *myeloid tissue* is characterized by its morphological heterogeneity and variegation. This is due to the coexistence of two essentially different groups of cells, namely, those of the erythroblastic group and those of the leukoblastic group. Each of these groups is made up of an *infinite series of morphological transitions*, commencing in an undifferentiated cell with basophilic protoplasm and terminating in a highly differentiated end-product with specific microchemical properties. It is folly to attempt to

attach a special name to each cell representing a stage in this series of transitions. It is more important to be able to recognize the *trend of the transitions* and to be able to tell roughly how far the majority of the cells have progressed in their development. The transition pictures occur both in the erythroblastic and in the leukoblastic groups, but there is no crossing from group to group. The close proximity of the elements of each group to one another in the myeloid tissue probably accounts for the fact that marked proliferation of one group is always accompanied by signs of proliferation in the other group. The earliest recognizable stage of erythrogenesis is represented by a mononuclear basophilic cell devoid of hemoglobin. Nevertheless, the characters of the nucleus as well as those of the protoplasm are sufficient to differentiate these cells from the earliest recognizable cells of the leukoblastic series. Whether or not the earliest differentiable members of these two groups are preceded by a common parent cell is not known. Up to the present time, at least, there is no conclusive evidence in favor of a common direct parent of the erythroblastic and leukoblastic groups. In fact, what evidence there is favors an early independence and autonomous growth of the two groups.[3]

The appearance of newly formed myeloid tissue varies according to whether the hyperplasia is predominantly erythroblastic or leukoblastic. The erythroblastic type of myeloidosis is found in pernicious anemia, von Jaksch's anemia of children[4] in severe septic anemias, and in the regeneration following repeated losses of blood.[5] The leukoblastic type of myeloidosis is found particularly in myeloid leukemia and to a less degree in many infectious diseases.

Hyperplasia of the bone marrow is, of course, the most frequent example of local myeloidosis. When the hyperplasia of the bone marrow is inadequate, or, for reasons unknown, does not occur, or is prevented mechanically, myeloid tissue makes its appearance in the spleen and liver, sites in which it was present in intra-uterine life. Osteosclerosis is an example of mechanical obliteration of bone marrow followed by myeloidosis of the spleen and liver. In the spleen the myeloid tissue is found in the pulp and not in the follicles; in fact, progressive myeloidosis of the pulp encroaches on the follicular borders even to the point of practically complete obliteration of the follicular elements. In the liver, myeloid tissue is found either as intracapillary islands or as loose masses in the periportal spaces. Myeloid tissue is found less frequently in more aberrant sites: the *interfollicular* tissue of the lymph nodes, the *perifollicular* tissue of the lymphoid structures in the intestine, in

[3] Stockard, C. R.: Am. Jour. Anat., 1915, xviii, 227 and 525.
[4] Stillman, R. G.: A Study of von Jaksch's Anemia, AM. JOUR. MED. SC., 1917, cliii, 218.
[5] Skornjakoff: Deutsch. Arch. f. klin. Med., 1911, ci, 251. Milne: Jour. Exper. Med., 1912, xvi, 325.

the obliterated appendix, and in sites of pathological ossification, *e. g.*, laryngeal cartilages.

Typical pernicious anemia, with a high color-index and leukopenia, or typical myeloid leukemia, with a predominance of definite myelocytes, present no difficulties in diagnosis. It is the leukemias with a predominance of undifferentiated cells and the anemias with subleukemic blood pictures which necessitate extreme care in diagnosis and classification. A few cases will serve to illustrate these points.

CASE I.—*Acute myeloid leukemia with a predominance of undifferentiated non-granular cells.* I. A., female, aged five years, a patient of Dr. Frank Erdwurm, was taken sick on July 4, 1914, with pain in the right ankle, difficulty in walking, fever, bleeding from the mouth and nose, and progressive weakness.

Status on August 30. The patient is an emaciated child with a protuberant abdomen. The skin shows numerous hemorrhages varying in size from that of the point of a pin up to 1 cm. in diameter, and there are hemorrhages in the mucous membrane of the mouth. The teeth are normal. The heart is enlarged and there are signs of fluid in both chests and in the abdomen. The lower edge of the liver reaches to the umbilicus while the spleen extends to below that level. The superficial lymph nodes are all slightly enlarged.

The urine contained albumin and casts. The temperature varied between 100° and 104°. She was treated by cataphoresis, according to the method of Veraguth, and died on September 18, 1914. The blood examination showed 1,650,000 red cells with a hemoglobin of 31 per cent. and 99,000 white cells. The differential count was as follows:

Mononuclear non-granular cells	92.0 per cent.
Neutrophile myelocytes	2.7 "
Polynuclear neutrophiles	3.2 "
Lymphocytes	1.7 "
Mononuclear eosinophiles	0.2 "
Polynuclear eosinophiles	0.2 "

Two nucleated red cells of the megaloblastic type were seen while counting 1087 white cells.

The predominating cell is of extremely variable morphology. The average size is larger than that of a polymorphonuclear leukocyte, although smaller forms are numerous and extremely large forms are not infrequent. The nuclei are round or oval, frequently folded upon themselves or even highly convoluted with the preservation of their round or oval contour. The nuclei are grayish violet in triacid preparations. Nuclear figures (diasters) are present. Among these cells there are some which show immature and scanty neutrophilic granulation (Giemsa and Jenner stains).

The myelocytes are also extremely variable in morphology, mature forms being scarce. The mononuclear eosinophiles vary in size and degree of differentiation. Some of the granules are rich in basophilic substance. The red blood corpuscles show marked variation in size, shape, and hemoglobin content. There is slight polychromatophilia. Normoblasts and megaloblasts are present. Lymphocytes are present, though their recognition is difficult on account of the large number of small undifferentiated myeloid cells.

Conclusion. The blood is characterized by a preponderance of undifferentiated cells of the myeloid group. A complete series of transitions can be traced from non-granular mononuclear cells with basophilic protoplasm to fully differentiated myelocytes.

Diagnosis. Myeloid leukemia of myeloblastic form with extreme anemia.

CASE II.—*Atypical leukemia with anemia* (?) *or pernicious anemia with leukocytosis* (?) *so-called "leukanemia."* A. S., aged forty-two years, seamstress, German, was taken ill with toothache, swelling, and suppuration of the left cheek, from which she apparently recovered. She came to the hospital complaining of fatigue, buzzing in the ears, headache, and hemorrhage from the gums and into the skin. Physical examination showed extreme pallor of the skin and mucous membranes, hemorrhages in the skin, retina, gums, mouth, and tonsils, enlarged lymph nodes, and an enlarged spleen. There was progressive enfeeblement, a temperature running up to 103.5°, and nosebleed, terminating in death three days after admission to the hospital.

The blood showed 1,790,000 red cells and 45 per cent. hemoglobin, a color-index of 1.2. The white cells numbered 28,000. The differential count was as follows:

Mononuclear non-granular cells	67.4 per cent.
Mononuclears with imperfect scattered neutrophilic granules	11.4 "
Neutrophile myelocytes	6.3 "
Polynuclear neutrophiles	3.6 "
Lymphocytes	11.0 "
Mononuclear eosinophiles	0.3 "

One normoblast was seen for every 500 white cells.

Autopsy reveals enlarged lymph nodes, an enlarged spleen, and complete absence of bone-marrow hyperplasia. In the spleen and lymph nodes the follicles are well preserved and consist almost exclusively of small lymphocytes. The pulp of the spleen and the interfollicular tissue of the lymph nodes show extensive myeloidosis of the myeloblastic type. There is slight hemosiderosis of the spleen and the lymph nodes contain typical megakaryocytes. In the liver there is slight periportal myeloidosis and no hemosiderosis. The appendix is obliterated and shows extreme myeloidosis.

The question of primary anemia or primary leukemia in this case has been discussed before.[6] In spite of the severe anemia, with the high color index and the mild hemosiderosis of the organs, the predominantly leukoblastic type of hematogenesis is sufficient, in our opinion, to warrant the classification of this case as atypical leukoblastic leukemia.

CASE III.—*Osteosclerosis with extramedullary myeloidosis.* J. K., male, aged forty years, was admitted to the second medical division of Bellevue Hospital, having been taken sick on February 19, 1914, with sharp pain in the lumbar region. He quit work in April and from that time on spent most of his time in bed. He came to the hospital complaining of marked pain in the sternal region and dull, aching pain in the right leg. There were no gastric symptoms and no history of cancer. On examination the patient showed extreme pallor, some emaciation, and numerous subcutaneous nodules distributed over the abdomen and chest. There was no jaundice. Enlarged lymph nodes were found in the axillæ and groins. He lost eleven pounds in three months. A roentgenogram revealed the presence of osteoperiosteitis of the pelvis and the shaft of the right fibula. The patient became progressively weaker, and death took place six months after the onset.

The blood examination showed 3,000,000 red cells, 50 per cent. hemoglobin, and 9100 white cells. The differential count was as follows:

Polynuclear neutrophiles	44.0 per cent.
Myelocytes	11.0 "
Myeloblasts	6.0 "
Lymphocytes	23.0 "
Large mononuclears and transitionals	13.0 "
Eosinophiles	2.0 "
Mast cells	0.3 "

Six normoblasts were seen while counting 252 white cells.

The autopsy revealed scirrhous carcinoma of the stomach, with metastases in the pleura, pericardium, peritoneum, omentum, endocardium, myocardium, striated muscles, subcutaneous tissue, and bones. There was osteosclerosis of the osseous system, with obliteration of the marrow in the vertebræ. There was myeloidosis of the spleen and liver.

This case was variously interpreted by different clinicians as acute leukemia with leukemic nodules in the skin, as subcutaneous or metastatic endothelioma, and finally as von Recklinghausen's disease. All that the blood picture really permitted was a diagnosis of either irritative hyperplasia of the bone marrow or vicarious

[6] Meyer, Erich und Heineke, Albert: Ueber Blutbildung bei schweren Anämien und Leukämien, Deutsch. Arch. f. klin. Med., 1907, lxxxviii, 435. Butterfield, E. E.: Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz, Leber und Lymphdrüsen, Deutsch. Arch. f. klin. Med., 1908, xcii, 336.

leukoblastosis and erythroblastosis of the extramedullary blood-forming structures.

CASE IV.—*Purpura hemorrhagica, with severe anemia of a perni-cious type.* F. B., male, Spanish, aged twenty-five years, was admitted to the New York Hospital, history No. 202742, on November 3, 1915, complaining of fever, cough, and bleeding from the gums. His family history was negative, there being no knowledge of hemophilia or other familial disease. He has three healthy children, and his wife has had no miscarriages.

He does not recall the diseases of childhood, and denies all venereal infection. He always has been more or less subject to colds, cough, sore throat, and nosebleed, but has not been subject to prolonged bleeding from trauma or to bleeding from the gums. He has been losing weight for several weeks. His present illness began three weeks before admission. His chronic cough became acutely worse, and was accompanied by transitory pains all over his body and by rather severe substernal pain and chilly sensations. After a few days his condition improved so that he suffered only from a chronic cough, which was worse at night, and malaise and weakness. He raised but little sputum and had no hemoptysis. He has not been able to work since the onset of his illness. Twelve days before his admission he again became acutely ill, with fever and cough, but no chills, vomiting, or constipation. His condition continued about the same until the day before his admission to the hospital, when he began to have considerable bleeding from his gums. There was no other bleeding noted. He had some diarrhea a few days before admission, but does not know how long he has been pale or has had the rash.

Examination reveals a rather undersized, fairly well-developed and nourished man lying quietly in bed. He appears acutely ill, but is not dyspneic. The skin is warm, dry, very pale, and white. Small purpuric spots, 1 to 3 mm. in diameter, are very numerous over the feet and legs, less so on the thighs, trunk, and upper extremities. There is no cyanosis or jaundice. No hemorrhages can be seen in the mouth. The scleræ are white and the conjunc-tivæ pale. The eye-grounds are normal. The mouth and teeth are in poor condition. There is a moderate amount of pyorrhea and the gums are bleeding at the edges, but are not red or swollen. The tongue is protruded in the middle line, and is slightly tremulous and coated. The tonsils and pharynx are normal. Over the apex of the right lung posteriorly the fremitus is increased, and at the spine of the scapula there is tubular breathing and the voice and whisper are increased. No rales can be heard. The heart is not enlarged and no murmurs can be heard. The pulse is of good vol-ume and normal tension, regular in force and rhythm; the vessel wall is not palpable. The abdomen is negative. The liver and spleen are not palpable. There is no general enlargement of the lymph nodes.

Blood cultures and the Wassermann reaction were negative. The sputum was negative for tubercle bacilli. During the first week the temperature varied between 100° and 101°. For the first eight or nine days in the hospital the patient continued to bleed from the nose and throat, and there was considerable blood in the urine. The application of a tourniquet caused the appearance of a fresh number of purpuric spots. From November 8 to 15 there was at first constant diarrhea, with considerable bright red blood, and the urine contained blood. Later the blood in the stool became less and it disappeared entirely from the urine. The patient received 20 c.c. of horse serum on November 6 and 8, and he was transfused with citrated human blood on November 8, 9, 12, and 16, receiving a total of 348 c.c.

The blood examinations were as follows:

Nov.	R. b. c. per c.mm.	Hb. per cent.	Color index.	W. b. c. per c.mm.	Nucleated reds per c.mm.
5	3,810,000	80	1.1	9,600	0
9	1,900,000	40	1.1	15,000	0
11	820,000	25	1.6	28,000	5
13	880,000	21	1.2	26,000	41
15	840,000	18	1.1	30,000	20
17	1,010,000	25	1.3	26,000	9

Among the erythroblasts there are undifferentiated forms, with characteristic nucleus and intensely basophilic, hemoglobin-free protoplasm. Megaloblasts are present. This was a remarkable blood picture, bearing a close resemblance to that seen in pernicious anemia with a blood crisis. The patient gradually grew weaker and died five weeks after the onset.

Autopsy by Dr. William Elser. There are numerous petechiæ in the skin of the feet, legs, and forearms and a moderate number over the trunk, thighs, and upper arm. Panniculus is moderate and the superficial lymph nodes normal. There is blood about the nostrils and mouth. Pyorrhea is present. There are hemorrhages in the visceral pleura and pericardium. The heart is normal. The lungs are edematous, and there is a small hemorrhagic area in the upper portion of the lower lobe of the left lung. The spleen is small, weighing three ounces, and is normal in consistence. The Malpighian bodies are small and indistinct. The kidneys are normal in structure and size. The pelvis of the right kidney is completely filled with clotted blood, and there are hemorrhages in the mucosa of the bladder. The liver is normal in size, weighing three pounds three ounces. Its surface is smooth and brownish red, and consistence normal. The mesenteric and retroperitoneal lymph nodes are bluish black and dark red in color. The esophagus is normal. There are petechiæ in the stomach, small intestine, and appendix. The lymph follicles and patches are atrophic. The mucosa of the large intestine from the ileocecal valve to the anus

is swollen, dark bluish red, almost black in appearance. The folds and solitary follicles are necrotic. The intestines contain a dark brownish-red, foul-smelling fluid. The vessels running to and from the large intestine appear to be normal. The bone marrow of the upper third of the femur is light red in color, and almost diffluent in consistence. Here and there are small islands of fat. The marrow of the middle segment is of the usual fatty type. Cultures from the spleen are negative even by Rosenow's method. Cultures from the intestinal contents show no organism of the dysentery group. There was the characteristic histological picture of erythroblastic myeloidosis in the blood-forming organs.

The diagnosis in this case lies between *purpura hemorrhagica*, with the marked regeneration common to severe anemias of the pernicious type and *pernicious anemia* proper, with a crisis and complicating subcutaneous and submucous petechiæ. The dominant clinical symptoms as well as the serological findings (note) point to *purpura hemorrhagica vera*.

In the foregoing cases there were three instances of predominantly leukoblastic myeloidosis and one instance of predominantly erythroblastic myeloidosis, and in all cases there was an abundance of transition pictures in the blending between the cells of the predominant group. In these cases most of the cells have prototypes in fetal hematogenesis; cells which departed from the usual manifold transitions in the same groups in intra-uterine hematogenesis and which could possibly be interpreted as degeneration or involution forms were extremely rare. In some cases, however, the development of the white cells seems to take an aberrant course, and the blood picture is dominated by cells which have no prototype in embryonal blood formation; or, more strictly speaking, if such embryonal prototypes occur they are at least extremely scarce in the blood and blood-forming organs of the human embryo. It is very difficult to classify these cells, in which there appears to be a loss of coördination between the development of the nucleus and the differentiation of the protoplasm. A leukemic picture with a predominance of such cells has been described in chloroma,[7] and one of these unusual cases is briefly reviewed here. Two additional cases are also described, one showing a predominance of the same type of cell in a leukemic blood picture and the other a predominance of these cells in a leukopenic blood picture.

CASE V.—*Chloroma*. A. R., male, joiner, aged twenty-four years, caught cold four weeks before admission to the hospital and suffered from cough, toothache, and swelling of the glands of the neck. One week before admission he began to suffer from weakness, shortness of breath, and palpitation. He had much pain in the neck and intense salivation, and was able to swallow only liquid

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[7] Butterfield, E. E.: Beitrag zur Morphologie der Chloromzellen, Fol. hematol., 1909, viii. 179.

food. Four days before admission he became so weak that he was confined to bed. During the last two days numerous pin-point hemorrhages have appeared in the skin over the whole surface of the body. On examination the muscles were found to be poorly developed and the subcutaneous fatty tissue scant. There was general enlargement of the lymph nodes, which is extreme in both cervical regions. There were numerous petechiæ in the skin but none in the retinæ. The gums were thickened, loose, and bleeding. The heart was negative. The spleen was enlarged and firm. The edge of the liver was palpable, its dulness extending two finger-breadths below the costal margin. The temperature varied from 101° to 103°. The urine contained albumin and much iron.

The blood examination showed 3,400,000 red cells and 60 per cent. hemoglobin. The white cells were 60,000 and later rose to 200,000. The differential count was as follows:

Mononuclear cells, non-granular with convoluted nucleus	86.4 per cent.	
Mononuclear cells with imperfect and scattered neutrophile granules	7.0	"
Myelocytes	1.6	"
Lymphocytes	4.0	"
Mononuclear eosinophiles	0.4	"
Definite plasma cells	0.6	"

Two normoblasts were seen while counting 1000 white cells.

All transitions were seen from the dominant cell to the neutrophile myelocyte, while some of these cells showed scattered neutrophile and eosinophile granulations. The dominant cell was a peculiar one. The nuclear structure could be made out only with difficulty. When well stained the nucleus was seen to be folded and convoluted, often in a most intricate fashion. The protoplasm exhibited all grades of basophilia, and contained at times granules which were demonstrated with difficulty, but which reacted similarly to those seen in myeloblasts. The cells apparently belonged to the myeloid series.

The autopsy showed an enlarged liver and spleen and enlarged lymph nodes, which were definitely and distinctly green. There was no hyperplasia of the bone marrow of the femur or ribs. In the spleen the Malpighian bodies could not be recognized. There was periportal myeloidosis in the liver and interfollicular myeloidosis in the spleen and lymph nodes.

This case represents the last word in atypical leukemia, in that the dominant cell has no prototype in normal fetal or postfetal hematogenesis. While this same cell showed definite myelocytic transitions there was a total absence of hyperactivity on the part of the bone marrow, and the chief site of non-lymphocytic leukoblastic proliferation was in the *interfollicular* tissue of the spleen and lymph nodes.

CASE VI.—*General enlargement of the lymph nodes; leukemia; lymphatic tuberculosis.* I. B., male, Hebrew, aged forty years, was admitted to the New York Hospital, October 21, 1913. History No. 191055. He had always been well before the present illness. Twenty years before he had gonorrhea and a questionable lesion on the glans. Two or three months before admission he noticed hard, movable, non-painful swellings in his groins. One month before admission his wife and friends noticed that his abdomen was growing larger. He had no pain until one week before admission, when it began to be present, always under the right costal margin, coming on immediately after eating and lasting about five minutes. It was never severe. There was no nausea or vomiting. On examination the patient was seen to be well developed and nourished. He had slight pyorrhea. The tonsils were not enlarged. The lungs were negative. The heart was not enlarged, though there was a systolic murmur heard loudest at the apex and not transmitted. The pulse was regular and of good force. The lower edge of the liver extended 11 cm. below the xiphoid in the middle line. In the abdomen, above the umbilicus and to the left was a hard mass, about 6 x 9 cm. in size, the outer edge of which could be felt distinctly in the mammary line. The right edge could be felt through the rectus to the left of the umbilicus. There were no other masses. The spleen could not be felt. There was some shifting dulness in the flanks. There were collections of about six olive-shaped glands, about 4 cm. long, readily felt in each groin, and there were similar masses in both supraclavicular regions and axillæ. The urine contained no albumin or sugar. The Wassermann reaction was negative. The gastric contents contained no free hydrochloric acid, but did contain blood. There was a slight loss of weight during the patient's stay in the hospital.

Examination of the blood revealed the following:

Date.	R. b. c.	Hb., per cent.	W. b. c.	Non-gran. monos., per cent.
Oct. 21	6,400,000	87	68,000	75
24	5,100,000	90	101,000	89
Nov. 1	5,300,000	80	87,000	92

Most of the non-granular mononuclears showed a folded or convoluted nucleus and undifferentiated protoplasm. It is impossible to make out any transitions from these cells to any known elements in the human blood or blood-forming organs.

A lymph gland was excised, part of it examined histologically, and the remainder injected into a guinea-pig. The pig died in eighteen days, having developed extensive tuberculosis. The spleen and liver of this animal were injected in part into two other guinea-pigs, each of which developed tuberculosis, and died in the course of thirty days. The histological appearance of the excised node was

peculiar. There were round collections which resembled follicles on superficial examination. On closer examination they were seen to consist chiefly of cells with folded and convoluted nuclei similar to those seen in the peripheral blood. The interfollicular tissue consisted largely of the same type of cell; in fact, practically all the details of the normal lymphatic gland were absent. The appearance was not unlike a granuloma. The patient soon left the New York Hospital and went to the General Memorial Hospital, where, under benzol treatment, the leukocyte count was reduced from 50,000 to 10,000. From December, 1913, to July, 1914, the count varied between 10,000 and 20,000. The lymph nodes were reduced to one-third of their previous size. In July, 1914, in spite of benzol and roentgen-ray treatment, the count rose rapidly until it reached 60,000 on August 17, and the patient died a little over a year after the onset of symptoms. No autopsy was obtainable.

This case was obscure and indeterminate. The blood picture points to an atypical leukemia, while the histological and experimental data were indicative of a lymphatic granuloma, possibly tuberculosis. The long-sought relation between a leukemic blood picture and an infectious substrate may rest, unrevealed, in this case.

CASE VII.—*Obscure acute infection with atypical blood picture.* J. B., male, aged thirty-three years, was admitted to the New York Hospital August 9, 1915. His appendix had been removed six and a half years before. The onset of his present illness was marked fever, anorexia, and pain over the region of the liver. He felt weak and nauseated, and vomited at times. He had passed blood by rectum.

The patient was a large, well-nourished man, somewhat pale. The teeth were in fair condition and free from pyorrhea. The tonsils were enlarged and reddened. The lymph nodes were moderately enlarged, the epitrochlears were not palpable. The lungs were negative. The heart was enlarged and the pulse soft and dicrotic. The abdomen was negative except for the scar of his appendectomy operation. The liver and spleen were not palpable. There were scars over the tibiæ but no edema or tenderness.

The blood examinations showed the following:

Date.	R. b. c.	Hb., per cent.	W. b. c.	Non-gran. monos.	Polys., per cent.
Aug. 10	3,800,000	73	6800	98	2
20	....	..	7800		
Sept. 6	2,240,000	50	3800		

The non-granular mononuclear cells were in great preponderance and were essentially the same in type as those seen in Case VI. The polynuclear neutrophiles were almost absent.

The urine contained no albumin on admission, but on August 26 albuminuria appeared and remained until death. The temperature

ranged between 101° and 105°, usually above 104°. The lymph nodes enlarged so that by August 18 practically all the superficial nodes were distinctly swollen and the spleen and liver were palpable. There was a phlebitis in the left leg. The following day a pericarditis developed. On August 23 the phlebitis was diminishing and the gums were swollen and red, though not bleeding. By August 29 the gums became very sore and began to bleed, and the tonsils were much swollen. The following day there were signs of fluid in the left chest and 250 c.c. were removed. The fluid was pink in color and a culture revealed the presence of the Bacillus pyocyaneus. By September 1 the tonsils had so increased in size that they met in the middle line. On September 3 the chest was again aspirated and 400 c.c. of fluid removed. The Bacillus pyocyaneus was recovered from this specimen also. Roentgen-ray examination showed an enlarged heart and a mass of enlarged bronchial lymph nodes above it. The Wassermann reaction was negative and two blood cultures remained sterile.

Autopsy. The autopsy revealed a mass of enlarged bronchial lymph nodes, one gland measuring 3.5 cm. in length. The liver weighed 2400 gm. The spleen was enlarged. There was some perisplenitis and the follicles were not visible. The bone marrow was grayish yellow and somewhat gelatinous.

This case was by far the most obscure of all the atypical cases discussed. All of the familiar earmarks of an infection are present and the ordinary and the most refined methods of bacteriological search and analysis failed to reveal any known pathogenic organism. The cytological analysis showed a predominance of cells identical with the atypical cells of the two preceding cases, but the predominance in this case is only relative and the absolute number of all white cells was either normal or diminished.

These cases serve to illustrate the difficulty in diagnosis even with the aid of the most improved methods and with the histological evidence before us. They also illustrate the inadequacy of present therapeutic measures. Benzol, roentgen ray, faradization, transfusion, and splenectomy may produce fluctuations in the blood picture, and these fluctuations may be interpreted as improvements if one so desires; but the essential diseases of the blood-forming organs still run their usual course. This should not be a cause for pessimism and discouragement, but should stimulate to more active and consistent work until some fortunate group of workers find the clue which will throw some light upon the etiology of these conditions.

NOTE.—We are indebted to Dr. Witt for the results of the serological investigation. He was able to show that the greatly delayed coagulation time in this patient was associated with a diminution in the platelets, which numbered but 1000 per c.mm., and an increase in the antithrombin. The other elements in the coagulation reaction were apparently normal.

COAGULATION TIME OF BLOOD SPECIMENS FROM TUBERCU-
LOUS PATIENTS.

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Is there a relation between the tendency to hemoptysis which is exhibited by certain patients having pulmonary tuberculosis and the coagulation time of the blood? The answer to this question was the object of the investigation here recorded.

Hemoptysis, or bloody sputum, is understood to mean pure or nearly pure blood in considerable quantity, a teaspoonful or more, and not merely streaks of blood such as may come from an irritated throat.[1]

Some tuberculous patients and, according to Fishberg, a large proportion of cases of phthisis, pursue their course and terminate in recovery, or fatally, without any hemoptysis. Fishberg found a wide variation in the statistics concerning the frequency of this symptom during the course of phthisis, some reports stating 25 and others 80 per cent., with many figures intermediate.[2]

Other patients seem quite predisposed to hemoptysis and are characteristically known as "hemorrhage patients."

Our experiments were made during a period of six months, thus allowing for any possible seasonal influence, and also for the opportunity of selecting typical cases from the 300 patients treated in that interval at the North Reading State Sanatorium. Hemoglobin percentage was estimated in each case by the Dare instrument.

The coagulation time of the blood of each patient is used only on a comparative basis in these experiments. One must not expect to contrast the figures themselves with those obtained by another method. Cannon and Mendenhall[3] point out clearly that there is no definite coagulation time quite independent of the method used because the conditions peculiar to any coagulometer are likely to affect the time of clotting.

A consideration of the various methods which have been used in estimating blood coagulation time and their relative merits seem hardly necessary here. Addis reviewed this matter.[4] Cannon and

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[1] Cabot, Richard C.: Physical Diagnosis, 1910, p. 325.

[2] Fishberg, Maurice: Pulmonary Tuberculosis, 1916, p. 186.

[3] Factors Affecting the Coagulation Time of Blood, Am. Jour. Physiol., 1914, xxxiv, 225.

[4] Addis, T.: Coagulation Time of Blood, Quart. Jour. Exper. Physiol., 1908, i, 305.

Mendenhall[5] added still another method, based upon the principles laid down by Addis, and after they had gone over the work done by Addis and by Morawitz[6] on the various coagulometers.

We therefore were fortunate in being able to adopt Cannon's method, in which he eliminated the objectionable features mentioned in the criticisms by the foregoing authors in their discussion of the various coagulometers.

In the first place it is best to define the principles stated by Addis and approved by Cannon under which work of this sort must be carried on:[7]

1. The blood must always be obtained under the same conditions.

2. The estimates must all be made at the same temperature.

3. The blood must always come in contact with the same amount and kind of foreign material.

4. The end-point must be clear and definite and must always indicate the same degree of coagulation.

In addition to these four conditions, Cannon decided that the ideal instrument should yield a permanent objective record made by the blood itself.[8]

Our coagulometer was designed after the pattern of Cannon's but was somewhat modified in construction and working arrangement because the factors in our problem differed.

A brief description of the instrument used is as follows:

APPARATUS. The upright with attached balance beam of a prescription scales was set up on a small wooden stand. This platform rested on four leveling screws, which could be so adjusted as to bring the upright perpendicular, thus insuring proper equilibrium for the balance.

One arm of the balance beam was prevented from rising above a horizontal position by a check, a small brass lever operating at right angles to the beam, secured to a wooden upright. This check could be raised and lowered with a slight touch of the finger. At the opposite end of the beam was a ring to which could be easily hooked a short length of copper wire. This wire, 7 cm. long and 0.6 mm. in diameter (gauge 21 B. and S.) was bent above into a hook and below into a small ring slightly less than 2 mm. in diameter. The small ring would then rest in the cannula containing the blood in such a way as to allow for a descent of the wire through the blood to about 5.5 mm.

Eight of these wires were made up as nearly standard as possible, for when hung on the beam the weight of the wire, allowing for a counter-balance at the other end of the beam, made this end of the beam 60 mgm. the heavier.

The cannulas were fairly uniform in size and in capacity in accord-

[5] Loc. cit.   [6] Loc. cit., quoted by Cannon and Mendenhall, p. 225.
[7] Addis, T.: Loc. cit.   [8] Loc. cit., Cannon and Mendenhall, p. 226.

ance with Cannon's careful directions that all dimensions should
be as nearly standard as possible, so that the amount of blood[9]
received in them should be fairly constant and that the wire hanging
in the blood should present approximately the same surface in
different observations.

SIZE OF CANNULAS.

Outside diameter	3.5 mm.
Inside diameter	2.0 mm.
Length over all	23.0 mm.

The cannula rested nearly submerged in a water-bath at 25° C.
A rubber collar held the cannula from entirely slipping through
the hole in the bracket. The bracket was accurately adjusted to
allow for free descent of the wire and also for the proper submersion
of the cannula in the water-bath. A small circulation coil warmed
by an alcohol lamp kept the water-bath at uniform temperature.
Addis[10] insists upon the strict necessity of carefully fulfilling this
condition of constant temperature.

An electromagnetic signal which rang at half-minute intervals
completed the outfit.

DRAWING THE BLOOD. The blood was taken from the lobe of
the ear, which was previously cleansed with soap and water, alcohol,
and ether. The cannulas were cleaned in running cold water, then
passed through ether in order to destroy all traces of fibrin ferment
such as might remain from a former case.

The ear lobe was punctured with the point of a sharp bistoury
and the time then noted. This knife was cleaned with ether and
alcohol after each operation. Immediately as the blood drop
appeared the tip of the cannula was applied to the drop. Blood
quickly flowed into the cannula to within about 2 mm. of the
rubber collar.

The tip of the cannula was then sealed with plastiline, the cannula
set in the bracket in the water-bath, the wire hung on the balance
beam and inserted in the cannula.

The small ring would then be immersed in the blood. A thin
coating of liquid petrolatum, previously applied to the upper third
of the inside of the cannula, served two purposes. The oil covered
the surface of the blood, thus preventing contact with the air and
also lubricated the unfilled bore of the cannula so that the wire
would not stick to the side. Therefore the wire, in falling into the
blood at regular intervals represented the same weight each time.
In about thirty seconds from the time the ear was punctured the
cannula had been filled and placed in the water-bath, and all was
in readiness for operation of the apparatus.

OPERATION OF APPARATUS. This operation consisted of raising
the check with the finger at every half-minute record of the signal.
The other end of the beam, heavier by 60 mgm. would fall, allowing

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[9] Loc. cit., p. 227.　　　　　　　　　　[10] Loc. cit., p. 331.

the wire to sink into the blood. The check would than be lowered, causing the wire to rise and the beam to assume its usual horizontal position.

So long as the wire sank through the blood to the full extent of the 5.5 mm. play there was evidence that the blood was still fluid and that coagulation had not taken place.

END-POINTS. As soon as the blood clotted the weight of 60 mgm. was supported and the balance beam failed to move through its usual excursion. This phenomenon usually appeared suddenly— that is, the twelfth descent of the wire, for instance, would be unobstructed and as free as preceding movements; then at the next half-minute record the downward movement would be jerky and slow. The subsequent movement thirty seconds later would be interfered with and blocked; this recorded the end-point and testified to a sudden crisis of coagulation, which was confirmed by the jelly-like clot revealed on the wire ring and in the cannula when these were removed from the apparatus.

The coagulation time of a particular specimen of blood was measured by that interval elapsing between the time of puncturing the skin and the time when the end-point just described occurred.

RESULTS. One hundred and forty-eight specimens of blood were put through the apparatus for the determination of coagulation time. Sixteen of these trials produced variable results because the blood was obtained under dissimilar conditions—that is, the specimen in each case was taken from the needle of a syringe used in drawing a quantity of blood from the arm vein. The variable factors in this method of collection precluded the probability of approximately constant results in this group, and accordingly these 16 cases were thrown out.

Of the 132 remaining cases 12 represented second trials on the same patients. Therefore 120 different patients were considered.

Of the total 132, 65 gave a history of hemoptysis and 63 could not recollect this symptom.

Of the tuberculous, 47 were classed as closed and 73 as open cases, the former group including those without symptoms and with local signs practically quiescent, while the latter group represented patients showing one or another of the signs and symptoms of pulmonary tuberculosis.

The average coagulation time in 130 trials was seven minutes forty-five seconds. Two patients with open, semi-active pulmonary tuberculosis yielded specimens which did not coagulate within twenty-eight and thirty-four minutes respectively, and no end-points were observed. Each case was observed to have had recent hemoptysis. Four months later, after some improvement and no recurrent hemoptysis, one of these men presented a blood specimen which coagulated in six minutes. The other patient had left the institution in the meantime and no second specimen was available.

With the exception of these 2 cases the extreme increased coagulation time was twenty minutes forty-nine seconds recorded in 1 case. Between fifteen and twenty minutes only 1 case was recorded. These two men had no history of hemoptysis.

In the accompanying table the cases other than those above are grouped according to their recorded coagulation time:

Minutes.	Total.	Open cases.	Closed cases.	Cases probably non-tuberculous.	Cases with hemoptysis.	Cases without hemoptysis
15 to 14 . .	2	2	..	..	1	1
14 to 13 . .	3	2	1	..	2	1
13 to 12 . .	4	1	2	1	2	2
12 to 11 . .	6	4	2	..	3	3
11 to 10 . .	7	3	4	..	5	2
10 to 9 . .	16	14	2	..	8	8
9 to 8 . .	13	12	1	..	7	6
8 to 7 . .	15	8	7	..	9	6
7 to 6 . .	31	16	11	4	16	15
6 to 5 . .	14	3	10	1	6	8
5 to 4 . .	16	7	7	2	6	10
4 to 3 . .						
3 to 2 . .	1	1	..	..	..	1

A study of the data thus arranged discloses no gross evidence one way or the other of any relationship between the coagulation time of the blood and the tendency to hemoptysis.

SUBSTUDY. The history of hemoptysis was more or less remote in some of the 65 patients classed in this group. Accordingly, we selected 13 patients whom we had recently observed having had hemoptysis and determined the coagulation time of the blood in each case. The estimates were:

11 minutes		30 seconds
10 "		
9 "	40 "	
9 "	30 "	
9 "	30 "	
9 "	30 "	
9 "		
8 "	30 "	
6 "	30 "	
6 "	30 "	
6 "	30 "	
6 "		
5 "	30 "	

The first five records referred to patients who were having recurrent pulmonary hemorrhages, although not in any large quantities. The last record, five minutes thirty seconds, referred to a patient who daily expectorated from one to four ounces of blood.

This patient[11] has a history suggesting the aspiration of foreign bodies, probably one or more shoe-nails, and the physical signs

[11] Case No. 2272, North Reading State Sanatorium Clinical Records.

point to bronchial stenosis probably due to foreign body in the bronchus. His sputum is negative for tubercle bacilli and his daily hemoptysis for months is altogether too extraordinary to be explained as merely a symptom of pulmonary tuberculosis. Eliminating this case from the group the average time is eight minutes thirty seconds.

We then selected 12 non-hemoptysic patients, in each of whom the disease process could be assumed to parallel those of the first group. The records of coagulation time obtained were:

10 minutes	30 seconds
10 "	
9 "	30 "
9 "	30 "
9 "	30 "
9 "	
8 "	
8 "	30 "
7 "	30 "
7 "	
6 "	30 "
6 "	30 "
Average 8 "	30 "

Each case of the twenty-four in this substudy was one of advanced pulmonary tuberculosis with positive sputum.

As a matter of observation it seems that those patients far advanced in the disease and with active signs and symptoms have increased coagulation times. On the other hand, we obtained a record of six minutes thirty seconds, for instance, in a specimen from a patient who was a bed case with far-advanced disease.

In relation to this and other similar variations found in our results we must respect the warning which Addis sounds. He believes that the indirect method of determining blood-coagulation time will probably give untrustworthy results in pathological condition, due to the fact that the agglutination of the blood is increased in disease[12]—that is, the corpuscles may be agglutinated by their own serum, and thus agglutination may closely simulate coagulation.

Our coagulometer operates as an indirect method because the evidence that coagulation has occurred is deduced from the change in the physical character of the blood—that is, a loss of fluidity. Addis contrasts this method with the direct in which the end-point of coagulability is determined by the first appearance of fibrin.

Cannon's apparatus represents a combination of direct and indirect methods. The wire used in their experiments was counter-balanced at 30 mgm. while ours was at 60 mgm. We therefore doubled the weight to be supported by the coagulated blood when the end-point had occurred, and our reason for doing so arose from Addis's objection.

12 Addis: Loc. cit., p. 320.

It appears possible that even with using the heavier wire we encountered this obstacle of agglutination. All the necessary conditions were complied with carefully in order to ensure approximately constant results, and yet it must be admitted that the results shown are so variable as to invite serious criticism. We doubt if experimental error could be the entire basis of such criticism.

EXPLANATORY NOTES. We preferred the ear rather than the finger as a source from which to obtain the blood. In tuberculous patients the ears invariably yielded the specimen promptly, while the fingers, more or less subject to chronic passive congestion, were not so satisfactory in this respect. Addis found that blood differed very little, if any, in time of coagulation whether it was drawn from a deep or superficial source,[13] and that increased congestion, as would be produced by cleansing the ear lobe, made no difference.[14]

Addis found no diurnal variation in the coagulability of blood, the coagulation time of the blood of the same individual being constant at different times of the day and even on different days.

Addis used the first drop of blood to appear.[15] Cannon and Mendenhall found that the first few samples of blood taken from an animal showed rapid or somewhat irregular rates of clotting.[16]

In applying their method to testing human blood they found on one occasion that the first sample showed the largest variation in coagulation time from the average—that is, +0.6 minute, while the second and fifth samples showed the least — that is +0.1 minute. The average error was +0.3 minute.[17]

The samples of blood which we used in our experiments composed the first few drops drawn, and this blood was quickly introduced into the cannula within a few seconds of the time when it first appeared.

Special care was necessary in this operation to prevent any longer contact of the blood with the air. Moreover, no specimen was taken up from skin previously covered with recently shed blood. Addis[18] has shown conclusively the large experimental error arising from neglect of complying with this condition.

The puncture made in each case was sufficient to ensure the prompt appearance of the blood drop and also an approximately constant rate of outflow.

In drawing a quantity of blood from a vein into a test-tube for serological examination we have occasionally observed a much increased coagulation time in certain specimens. While this is an inaccurate method of determining coagulability, due to varia-

[13] Addis: Loc. cit., p. 330.
[14] Loc. cit.
[15] Addis: Loc. cit., p. 315.
[16] Cannon and Mendenhall: Loc. cit., p. 231.
[17] Ibid.   [18] Addis: Loc. cit., p. 315.

tions in temperature and in conditions influencing the contact of the blood with foreign surfaces, yet the difference in clotting times have often been extraordinary.

Upon examining later the contents of such tubes we have found in some a clotted mass of serum, "chicken-fat" clots, of tough, white, fibrous consistency. These specimens were common to pathological cases with advanced disease. Whether or not the formation of this so-called "serum clot" may have a bearing upon the agglutinative process simulating blood coagulation we leave to conjecture.

SUMMARY. 1. One hundred and twenty patients yielded one hundred and thirty-two specimens of blood for the estimation of coagulation time. Of these patients 8 were probably non-tuberculous. The rest were afflicted with pulmonary tuberculosis, 73 being open and 47 closed cases. Of the 120 patients 54 per cent. gave histories of hemoptysis.

2. The average clotting time was seven minutes forty-five seconds.

3. Grouping these cases in tabular form according to:

(a) Coagulation time,

(b) Occurrence or non-occurrence of hemoptysis, and

(c) Stage of disease activity or quiescence, we find no striking demonstration of results.

4. A substudy of 24 cases was made. Twelve patients with recent hemoptysis showed coagulation times increased in several instances and in average time eight minutes thirty seconds. Twelve patients without hemoptysis and with disease processes parallel to those of the patients in the first group showed coagulation times increased in as many instances as among those of the first group. Average was the same, eight minutes thirty seconds.

5. The indirect method of determining blood coagulation time may produce variable results when applied to pathological conditions.

6. No attempt was made to show the results of medication with calcium salts. Addis found that the coagulation time[19] of the blood was unaffected by the administration by mouth of soluble calcium salts. In a notable study[20] Addis found that the amount of ionizable calcium in the blood is increased by giving soluble calcium salts by mouth but the increase which is brought about is considerably less than is necessary before any appreciable effect is produced on the coagulation time.

[19] Addis: Loc. cit., p. 332.
[20] Addis, T.: Quart. Jour. Exper. Med., January, 1909, ii, 163.

SUBACUTE AND CHRONIC NON-TUBERCULOUS PULMONARY INFECTIONS.*

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For a number of years I have been very much interested in a class of cases that have come under my observation from time to time, with very definite localized physical signs in the chest closely simulating pulmonary tuberculosis, the diagnosis of which disease has frequently been made, but in which a close study of the clinical findings and the subsequent course did not seem to justify this conclusion. When my attention was first directed to these cases the literature contained no references that I was able to find that seemed to fit in with their clinical aspect; but quite recently several American writers have described conditions which in some respects coincide entirely with mine, and which, taken together with my experience, appeared to furnish a basis for a distinct clinical entity. These cases have been variously described as "a lobar form of bronchopneumonia," "a localized subacute form of bronchopneumonia," and as "chronic non-tuberculous pulmonary infections."

Lord,[1] in 1902, and later in 1905, described in detail various infections of the respiratory tract due to influenza bacilli which were frequently confused with pulmonary tuberculosis. While most of his cases presented signs of disseminated bronchitis, or of localization at the pulmonary apices, two or three of them corresponded in their clinical features fairly well with some of those which I here present.

In 1913 Riesman[2] described a lobar form of bronchopneumonia of long duration occurring in children and young adults. He reported 7 cases in detail, and stated that he had seen at least as many more.

Larrabee,[3] in 1915, reported 17 cases of which the characteristics were very similar to those described by Riesman. In both of these series the essential features were described as those of a subacute lobular pneumonia, with lobar distribution, occurring in one or the other of the lower lobes, usually of several weeks' or months' duration, sometimes with low fever, at others with no constitutional symptoms whatever, but tending gradually to complete recovery. No autopsies were reported. Larrabee reported roentgen-ray examinations in 6 cases, in 4 of which there were increased densities in the lower lobe, less intense and less circumscribed than in lobar pneumonia, and in the other 2 cases the roentgen-ray picture was normal. Neither of these observers systematically determined the

character of the infecting organism, but both state that pneumo-
cocci predominated in the cases in which the sputum was examined.
Both also found a very slight degree of leukocytosis in many of the
cases which, however, was not constant.   The cases reported by
these two observers correspond to those which we will describe as
a subacute type of non-tuberculous pulmonary infection.

Very recently Hamman and Wolman,[4] and after them Garvin,
Lyall and Morita,[5] reported on a condition characterized by them
as a chronic non-tuberculous pulmonary infection.   The findings
of these observers are very well in accord with each other and with
some of the cases which will be here reported.   In both of these
studies great emphasis was placed upon the frequency with which
these cases were confused with those of pulmonary tuberculosis.
The characteristics were those of a chronic cough and expectora-
tion, with periodic exacerbations, frequently with hemoptysis,
extensive physical signs almost invariably affecting one of the
lower lobes, and strikingly little impairment of the general health.
Hamman and Wolman, from the physical signs and from the results
in the 1 case which came to autopsy, described the pathology as
a localized bronchitis with infiltration of the bronchial wall and
foci of bronchopneumonia about the smaller bronchi.   They stated
that the infecting organism was most commonly the pneumococcus,
less often the influenza, and still less frequently various types of
streptococci.   Garvin and his associates studied the infecting organ-
isms very carefully, and came to the conclusion that the influenza
bacillus was the chief offender in the majority of their cases, being
found in 7 out of the 8 cases reported, and predominating markedly
in 4 of the 7.   In 2 cases types of the streptococcus predominated.

The course of the disease is described as marked by extreme
chronicity, the symptoms of which go on more or less continuously,
but in which the intensity is varied by frequent remissions differing
materially in their severity.

Garvin, Lyall and Morita lay stress upon the value of postural
treatment in these cases, for the alleviation of the symptoms and
also for intensifying the physical signs and obtaining specimens of
sputum for actual bacteriological investigation.

The series of cases which I have to report, 22 in number, represent
a portion of a considerably larger number which have been observed
in the past few years.   These particular cases are reported because
of the facilities they have afforded for close study and not from any
selection because of their special clinical features.   They appear
to fall into three distinct groups, which, however, fuse to a greater
or less degree into each other, and which, when taken as a whole,
and when also correlated with the reports of the observers already
quoted, appear to form one distinct class of cases which deserves
a place as a separate entity, and for which, employing an amplifi-
cation of the designation suggested by Hamman and Wolman, the

term "subacute and chronic pulmonary infections" seems justified. The cases will be considered under three groups: (1) the subacute type; (2) the subacute type with recurrences; (3) the chronic type.

SUBACUTE TYPE. Nine of the 22 cases here reported are included in this type. These cases are characterized by a subacute onset often with coryza, but with marked cough and expectoration the predominating symptoms. The constitutional disturbance with fever is moderate and of short duration, usually two to four days, or may even be absent, after which the patient promptly regains the normal feeling of good health, but the cough and expectoration persist for several weeks or a few months. Hemoptysis may occur (Case I). There is no pain.

The physical signs are very characteristic and vary remarkably little in the various cases. They are almost always confined to the whole or greater part of a lower lobe, and consist of slight dulness, somewhat impaired vesicular murmur, and subcrepitant and moist rales intensified by cough. In one case (Case V) the signs were at first over one entire lung, but later localized in the lower lobe. Sometimes, if seen early, a coryza may be present, and occasionally a few scattered sibilant rales may occur in other portions of the chest for a few days. Signs of pleurisy were found in 2 cases, in 1 of which (Case IX) there was a slight pleural effusion—the only one of the entire series.

The course of the disease in this type is a gradual disappearance of cough and expectoration, followed later by the complete loss of all physical signs, and ending in perfect recovery in a period varying from six weeks to four months.

Sputum Examination. The sputum is profuse and mucopurulent and persistently negative for tubercle bacilli. Cultures from the sputum were made in 8 of these cases and showed influenza bacilli in marked predominance in 5, pneumococci group IV in 2 and streptococcus viridans in 1.

Roentgen-ray Examination. Roentgenograms were made in 7 cases; in 3 they were normal, in 3 others there was some intensification of pulmonary markings in the lower lobes, not necessarily most marked on the side of the lesion, and in 1 there was a slight pleural effusion.

SUBACUTE TYPE WITH RECURRENCES. Six cases of the series are included in this type. These cases present the same clinical picture as those of the preceding type, run a similar course and apparently recover as they do, but have been observed upon two or more separate occasions to have gone through the same cycle with an intervening period during which all signs and symptoms are absent. The striking observation during the recurrences is the fact that the physical signs reappear in the same portion of the lung as in the previous attack, giving basis for the assumption that the condition is a recurrence and not a new infection.

The symptoms, signs, and course of these cases, both in the original attack and the recurrence, are the same as before described. And this type also presents lesions always in one of the lower lobes.

Sputum Examination. Tubercle bacilli are uniformly absent. Cultures of the sputum were made in all 6 cases and in 3 of them in two separate exacerbations. Four of these cases originally showed pneumococcus type IV and 2 of them influenza bacillus. In the 3 cases in which later cultures were made during separate exacerbations, all of them originally showed pneumococcus type IV; on the second examination one of these again showed this organism, the second showed pneumococcus type II B, and the third influenza bacillus.

Roentgen-ray examinations were made in 5 of these cases and showed no abnormalities in 4 and slight intensification of the pulmonary markings in 1 at the site of the lesion.

CHRONIC TYPE. Seven cases of the series are here included. The distinction in type is made upon the fact that at no time while under observation have the abnormal signs disappeared, but, on the contrary, have remained fairly constant, although the predominating symptoms of cough and expectoration were subject to distinct exacerbations, so that symptomatically they closely resemble the former types.

In all essential features the signs and symptoms during the exacerbation correspond to those already described for the other types, but there exists a greater tendency to a more constant cough and occasional run of slight fever, and in two instances some tendencies to impairment of general health have been noted. In general, however, as in the previous instances, the general state of health and nutrition was maintained at practically a normal level. One case (Case XVI) has gone through a pregnancy uneventfully and is at the present time again pregnant in the seventh month and remains in good physical condition. In 4 cases pain in the affected side of the chest was a marked symptom.

One of these cases has been under observation seven years, another four years, and the others, with one exception, from two to three years.

Sputum Examinations. Tubercle bacilli were always absent in very numerous examinations. Cultures were taken usually during an exacerbation of the cough and expectoration in all 7 cases, and in 2 of them in two different exacerbations. Four showed pneumococci type IV, 3 of which showed the same on the second examination and the other influenza bacilli on the second. The other 3 cases showed Streptococcus viridans in predominating numbers.

Roentgen-ray examinations were made in 6 of these 7 cases. All showed abnormalities chiefly characterized by distinct accentuation of the pulmonary markings in one or both lower lobes, or as in

1 case throughout the entire lung. One showed a diffuse clouding as of pleuritic thickening, two irregularities of the diaphragm under the lesion, ascribed to adhesions, and in another the heart was displaced toward the side of the lesion, presumably by adhesions.

SUMMARY.—*Sex.* When we consider the reports of all three types of this condition together we find that of the 22 cases 8 were males and 14 females. The predominance of females is probably a mere accident of no significance.

Age. The age incidence at the time of first observation varied from seven to sixty years, with the majority in full adult life, that is, from thirty to fifty years. The subacute cases, however, occurred with one exception before the age of thirty, and taking into consideration the probable incidence of the condition from the history of the other cases we find that the great majority had their first symptoms before the age of thirty-five. It is to be noted that of the 7 chronic cases, 4 began after the age of thirty, indicating that perhaps this type is more apt to occur in older persons, although this is not the case in Hamman and Wolman's cases nor in those reported by Garvin and his associates. From the experience of the subacute cases, and from several other cases in children which I have observed, but which are not here reported, I am inclined to agree with Riesman that when this condition occurs in younger persons prompt and complete recovery is the rule.

Seasonal Incidence. The time of year in which these infections occurred could be accurately determined only in the subacute cases. In the 15 cases of this type the original attacks occurred with much greater frequency during the colder months of the year. The date of the onset in 12 of these 15 cases was during the months from October to April inclusive. In the cases with recurrences 8 of such recurrences are reported, and 7 of these occurred also in this same period from October to April.

Site of the Lesion. The location of the physical signs was in the left lower lobe in 13 cases, in the right lower in 5, in both lower lobes in 3, and in the entire right lung in 1. In the cases of recurrence the signs returned in their original location excepting in one instance.

Cough and expectoration were the predominating features in all cases.

Pleurisy was not a frequent finding. Slight friction sounds were found in 2 cases and slight pleural effusion in 1 other. Three other patients complained of considerable pain in the chest on the side of the lesion, and these were all cases of the chronic type.

Hemoptysis. Frank hemoptysis occurred in 2 cases and bloody sputum at times in 4 others.

Bacteriological Findings. Very numerous and repeated examinations for tubercle bacilli were made in all cases, with negative results.

Specimens of sputum, obtained with particular care in order to get so far as possible the secretion from the lung uncontaminated with organisms from the upper air passages, were taken in all of the cases of the series excepting 1. These were studied both by direct smear and by cultures on various media. In a large number of cases also they were passed through white mice and smears and cultures were made by Dr. Avery in accordance with the technic developed at the Rockefeller Institute. The results of these cultures showed pneumococcus type IV, predominating in 10 of the 21 cases, influenza bacilli in 8, and Streptococcus viridans in 3. In 3 cases of the series in which pneumococcus type IV predominated on the first examination the opportunity was offered for later cultures during a subsequent recurrence. In one of these pneumococcus type IV was again obtained; in another pneumococcus type II B in practically pure culture; and in the third the sputum during the second attack showed influenza bacilli in marked predominance. In many of the cultures comparatively few colonies of other organisms were present, such as Staphylococcus aureus and Streptococcus mucosus. Two of the cases in which the Streptococcus viridans predominated were cases of the chronic type.

Roentgen-ray Findings. Eighteen cases of the entire series were studied by means of the roentgen-ray. The most striking feature of these photographs was the insignificant changes shown when compared with the extent of the physical signs. In 7 cases the plates were entirely normal, in 1 the plate was normal except for evidence of pleural effusion, in the 10 others the chief abnormality to be noted was an increase in density of the normal pulmonary markings, most marked in the lower lobes, but not necessarily confined to the affected side. These changes are similar to those noted in cases of chronic bronchitis or in chronic pulmonary congestion secondary to cardiac disease. They in no way whatever have any resemblance to the picture shown by tuberculous infiltration which is in striking contrast to the physical signs which closely resemble each other in these two conditions.

In 4 of this last group of cases there was in addition to the intensified markings some evidence of pleuritic adhesions. These 4 cases were all of the chronic type.

It is to be noted that all of the chronic cases examined by the roentgen-ray showed some change while in the subacute types, whether with or without recurrences, the majority of cases were normal upon roentgen-ray examination.

DISCUSSION. There is a striking similarity between these three types of cases. The clinical picture of the original attack coincides in every respect with that later found either in the recurrence of the infection or in the exacerbation of the chronic case. The symptoms, the physical signs, the site of the lesion as well as the bacteriological and roentgen-ray findings do not materially differ. The

differences are principally in the further course of the disease, that it may clear up more or less promptly or may recur after an interval of months or more, or, lastly, may continue as a constant chronic condition marked by periods of exacerbation.

In the subacute type it is easy to recognize the same condition which was described by Riesman and Larrabee. In the chronic type we have all of the essential features of the cases reported by Hamman and Wolman and by Garvin, Lyall and Morita. The subacute type with recurrences is the link between the two. It seems quite evident that in all three types we are dealing with the same disease. It would appear probable that, as further opportunity to watch the subacute cases is afforded, many of them may recur, and that of these not a few may drift into the chronic type, for already one or two of the cases which have evidenced several recurrences show a tendency to a longer persistence of physical signs in the later attacks.

The pathological basis of the condition is incomplete, for the disease is not a severe or fatal one. The only available postmortem findings are those of the case reported by Hamman and Wolman, which showed the bronchi of both lower lobes dilated and filled with pus, with areas of bronchopneumonia about them. Both Riesman and Larrabee considered the condition to be one of subacute bronchopneumonia.

The evidence which we have to offer from the roentgen-ray does not indicate that there could be very much actual pneumonia in these cases, and this is in harmony with the absence of the physical signs of consolidation.

With due regard to the hazards attending the interpretation of slight variations from the normal roentgen-ray picture of the lung it is at least suggestive that the intensification of pulmonary markings occurred most uniformly in the chronic cases, and that in these evidences of pleural involvement by adhesions were presented. It was in these cases only that pain was a marked symptom.

It is suggested that the pathology of the condition may consist of a localized bronchitis with lobar distribution involving the submucous and peribronchial tissues of the bronchi. This may clear up or persist in a latent subacute form, offering a site predisposed to the recurrence which in turn increases the tendency to the production of fibrous tissue. This is the permanent condition in the chronic type, and with it may be associated a bronchopneumonia, the occurrence of which may explain the periodic exacerbations with fever. This corresponds closely to the pathological conception of the condition expressed by Hamman and Wolman.

It seems very probable that some of these cases may later develop into chronic interstitial pneumonia or bronchiectasis, although I have never personally observed such a development.

Considering the nature of the bacterial infection our findings are

in harmony with the reports of the other observers as to the predominating organisms cultured from the sputum. As already stated, Riesman, Larrabee and Hamman and Wolman all laid stress upon the pneumococcus as probably the important infecting agent, with influenza of secondary importance. Garvin, Lyall and Morita, however, found the Bacillus influenza the predominant infection in their chronic cases. As in our observations in the chronic type they also found varieties of streptococcus playing a part in some of their cases.

The higher percentage of predominating pneumococcus cultures found in our series may be due to the fact that it includes a large proportion of subacute cases, the bacteriology of which may differ from that occurring in the chronic forms studied by Garvin, Lyall and Morita.

The reappearance of physical signs in the same portion of the lung in different recurrences raises the question as to whether these recurrences are due to new infection from without or to recrudescences of the same infection which may lie dormant in the lung. That it may be a new infection is suggested by the fact that in 2 of our cases observed in separate attacks, organisms were found which differed from those first obtained. In order to throw light upon this phase of the problem in a number of pneumococcus cultures which were passed through mice the spleens of the animals were sealed and preserved in the hope that during a second attack the opportunity might be offered to compare the reaction of the two cultures to immune sera. Unfortunately for our object such recurrences in these particular cases have not occurred.

Another interesting feature is the fact that 4 of our cases occurred in pairs, 2 each in the same family, 1 case following the other, so that the probability of communication of the infection between them is very great. In the first pair the organism recovered from the culture was influenza bacillus in almost pure culture. In the second instance both influenza and pneumococcus type IV were recovered. In the original case of this pair the pneumococcus type IV predominated, in the secondary case the influenza predominated. At the time the cultures were taken the first case had already passed the acute stage, which may have influenced the results of the sputum cultures.

DIFFERENTIAL DIAGNOSIS FROM PULMONARY TUBERCULOSIS. That this condition offers many points of similarity to pulmonary tuberculosis is evident. The practical demonstration of this is afforded by the fact that very many of them first came under observation after having been diagnosed as tuberculous by competent observers. The chief points which serve to distinguish them from tuberculosis may be summarized as follows:

1. Complete absence of severe constitutional symptoms with the retention of excellent general condition in spite of the presence of extensive lesions.

2. The localization of the lesion with almost constant uniformity in one or both of the lower lobes.

3. The disappearance of all physical signs within a few months in the subacute cases.

4. The lack of progression of the lesion from its original site to other parts of the lungs.

5. The absence of tubercle bacilli in the sputum over long periods of time and the presence of other infectious organisms in predominating numbers.

6. The character of the roentgen-ray picture, which in these cases shows either nothing abnormal or very slight changes.

I wish to acknowledge my deep obligation to Dr. Oswald T. Avery not only for his great courtesy in making many painstaking bacteriological examinations, but also for his valuable advice upon many problems arising in the course of this study.

SUBACUTE TYPE.

CASE I.—A. G., male, aged twenty-two years, first seen August 1, 1913.

Previous History. The patient has not been subject to colds. He has been well excepting in the past year, when he had pain and vomiting and other digestive symptoms, for which a diagnosis of ulcer of the stomach had been made.

Present History. Four weeks previously, after rather hard exercise, he felt feverish, developed a slight cough, and his temperature was at 100° or 101° for ten days. He had no pain. Since then he has run a slight temperature, 99° or 99.5°. Two days previously he had had a distinct hemoptysis, about 3 drams. A diagnosis of pulmonary tuberculosis had been made by his physician.

Physical examination showed a slight dulness over the right lower lobe, with diminished breath sounds and numerous moist rales.

Course of the Disease. August 20 these signs were markedly diminished and the cough and expectoration much less. When seen on November 18, they had entirely disappeared. When last seen, January 1, 1914, the patient was in ordinary health and had resumed his normal occupation. There were no signs in the chest. His physician reported (1917) that he has continued perfectly well ever since.

Sputum culture showed influenza bacilli in almost pure culture.

Roentgen-ray examination was not made.

CASE II.—G. (brother of Case I), aged twenty-four years; first seen August 1, 1913.

Present History. The patient had had a cold in the head, cough and expectoration for ten days, with no fever, and he had kept at his ordinary occupation. The cough and expectoration were marked.

Physical examination showed numerous moist rales over the left lower lobe.

Course of the Disease. The symptoms subsided in two weeks. No opportunity for further examination was offered. His physician reported (1917) that he has had no further symptoms referable to his chest.

Sputum examination showed influenza bacilli in almost pure culture.

Note. A domestic in the same household as these 2 cases was sick with la grippe and bronchitis at the same time. Opportunity was not offered to examine her.

CASE III.—J. F., female, aged twenty-three years; first seen December 18, 1916.

Previous History. The patient had been subject to colds and cough in the winter, but they were never serious.

Present History. She had a cold in the head which began in October, 1915, and a cough developed a month later. Cough and slight expectoration had persisted ever since. Three days before she was first seen she had a slight fever and soreness in the left chest. There had been slight loss of weight and some malaise for the past month, but the patient had kept at her work regularly. She thought she might have had a little fever during the past few days. A diagnosis of pulmonary tuberculosis had been made.

Physical Examination. Normal percussion note; slightly diminished breath sounds with fine subcrepitant rales over the entire left lower lobe.

Course of the Disease. The patient was kept quiet in the open air for a week, at the end of which time the symptoms were less, although the signs persisted. She went away to the country for three weeks and then came back feeling perfectly well. She was last examined January 29, 1917, when the signs had entirely cleared up excepting for a few rales at the extreme left base. The patient has been well and at work ever since, with no symptoms.

Sputum examinations were persistently negative for tubercle bacilli. Cultures were not made.

Roentgen-ray examination, December 19, 1916, showed peribronchial thickening in the lower lobe, most marked on the right side.

CASE IV.—I. G., male, aged forty-five years, first seen December 15, 1915.

Previous History. The patient had always been well.

Present History. Five weeks previously the patient had developed a cough, with expectoration, without fever, and without any constitutional symptoms. He had kept at work regularly. A diagnosis of tuberculosis had been made.

Physical Examination. Over the entire right lower lobe there was slight dulness, diminished breath sounds, and numerous subcrepitant rales.

Course of the Disease. The patient went to Lakewood and led an open-air life. Three weeks later, on his return, he was much improved. The cough and expectoration had disappeared. The signs were then confined to a small area at the extreme right base. He has not been seen since.

Sputum examinations have always been negative for tubercle bacilli. Culture (Dr. Avery) taken January 4, 1916, showed influenzæ and pneumococci type IV, influenzæ predominating.

Roentgen-ray examination, December 15, 1915, showed slight peribronchial thickening in both lower lobes particularly on the right side.

CASE V.—W. V., male, aged sixteen years, first seen October 3, 1916.

Previous History. The patient had always been subject to colds.

Present History. In August, 1916, he contracted a cold, beginning with coryza, and since then has had cough and expectoration. There has been no fever or night-sweats or loss of weight; excepting for the cough and expectoration, the patient feels perfectly well, but had been told that he had tuberculosis.

Physical examination showed numerous subcrepitant rales over the entire right chest, most marked over the right lower lobe but also heard over the upper lobe. There was slight diminution of vesicular murmur and very slight dulness at the extreme right base.

Course of the Disease. The patient was kept quiet in the open air in Lakewood, and on his return, November 13, the signs in the chest had disappeared except in the right lower lobe, where there were scattered subcrepitant rales. December 19 the patient reported that the cough and expectoration had entirely disappeared several weeks previously, and on physical examination the signs in the chest had also diappeared. Since that time the patient has been entirely well.

Sputum examinations were negative for tubercle bacilli on two occasions. Culture showed Streptococcus viridans predominating, with few Staphylococcus aureus.

Roentgen-ray examination, October 3, 1916, showed a slight increase of the pulmonary markings throughout the right lung, more marked in the lower lobe.

Roentgen-ray examination, December 19, 1916, showed still somewhat increased pulmonary markings in the right lung, but less marked than previously.

CASE VI.—M. M., male, aged thirty years, first seen November 27, 1915.

Previous History. He had had a syphilitic infection two years previously and one very protracted cold, with bronchitis, eighteen months previously. He had kept at his usual work.

Present History. For one month he has had a cough, with marked expectoration, which began with a coryza. There were no other symptoms.

Physical examination showed very numerous moist rales over both lower lobes, more marked on the left side, with a few sibilant rales in the rest of the chest; also an acute coryza.

Course of the Disease. The patient was put in bed for ten days. He had no fever. The cough and expectoration gradually diminished, and on December 6 the signs in the right chest had entirely disappeared, but there were localized rales and slight dulness over the entire left lower lobe. After that he went to the country. He was last seen on March 1, 1916, when the chest was entirely clear.

Wassermann test was made December 18, 1915, +++. At that time he was put on specific treatment. The signs in the chest had already begun to disappear.

Sputum examinations were persistently negative for tubercle bacilli. Culture December 6, 1915, showed pneumococcus type IV predominating, with some Staphylococcus aureus.

Roentgen-ray examination November 27, 1915, showed nothing abnormal in the lungs.

CASE VII.—M. C., female, aged seven years, first seen February 29, 1916.

Previous History. In October, 1915, she began with a cough which developed into whooping-cough, which gradually subsided and the child returned to school the first week in January.

Present History. January 15 she again began to cough severely and raised considerable quantities of sputum. These symptoms continued up to the time of the examination and the child seemed pale and a little languid, but apparently had no fever.

Physical examination showed normal breath sounds in the left lower lobe, with numerous subcrepitant rales. Scattered over the upper left lobe and the entire right chest there were sibilant rales, with a few fine subcrepitant rales at the right base.

Course of the Disease. March 7, 1916, these signs had entirely disappeared excepting for localized rales over the lower three inches of the left posterior chest, with somewhat diminished breathing. March 7 these signs had entirely disappeared. The patient in the meantime had lost the cough and was feeling and acting well.

Sputum examination (Dr. Avery) March 1, 1916, culture showed influenza markedly predominating; a few Streptococci mucosus.

Roentgen-ray examination, February 29, 1916, showed enlarged glands at the root of the lung on the right side; slight infiltration extending inward from this into the parenchyma; bases normal.

CASE VIII.—I. L., female, aged twenty-one years; first seen April 2, 1917.

Previous History. Right apical tuberculosis discovered in October, 1915. The patient had been at Stony Wold Sanatorium for ten months, and since that time had been at home. She had not gone back to work but had been feeling perfectly well.

Present History. Three weeks ago she had had what she thought was la grippe. She was confined to bed with fever and a bad cough with expectoration for a week. Since then the cough and expectoration have been very marked and have continued up to the present time. She was seen by the physician who had previously treated her for tuberculosis, and was told that she had an acute tuberculosis of the left lower lobe, and artificial pneumothorax was advised.

Physical Examination. There was marked dulness and marked vesicular breathing; numerous moist rales over the entire left lower lobe. A few friction sounds at the axilla. There was slight dulness and prolonged high-pitched breathing at the right apex.

Course of the Disease. The patient is still under observation. The physical signs are the same. The cough and expectoration are very much less. The patient already feels perfectly well and wants to return to work.

Sputum examination was negative for tubercle bacilli.

Culture (Dr. Avery) showed pneumococcus type IV predominating with some influenza.

Roentgen-ray examination April 2, 1917, showed a few calcified tubercle bacilli at the right hilus and up toward the right apex. The lower lobes of both lungs were absolutely normal.

CASE IX.—J. L., female, aged twenty years; first seen April 17, 1917.

(This patient is a sister of Case VIII; she is particularly interesting because she was taken ill shortly after her sister with very similar symptoms.)

Previous History. Patient had always been well; not subject to coughs and colds.

Present History. Ten days previously she went to bed feeling chilly and feverish and with a sharp cough. There was no coryza. She stayed in bed with considerable cough, but no expectoration, for a week. For the past three days she has been feeling very much better. The cough has continued, with some expectoration. The patient is now up and about. There was no pain in the chest.

Physical Examination. Over the entire left lower lobe there is dulness merging to flatness at the base, with an area of distinct bronchial and voice sounds at the left axilla. Above this area and extending upward two inches above the angle of the scapula, the breath sounds were somewhat diminished, and there were numerous crepitant and subcrepitant rales. The chest was explored and a few cubic centimeters of slightly cloudy pale serum were obtained. On examination this fluid was sterile. Differential cell count showed large mononuclears 63 per cent., small mononuclears 27 per cent., polymorphonuclears 9 per cent.

Leukocytes 13,800, polymorphonuclears 75 per cent.

Course of the Disease. The patient improved rapidly, and when last seen, April 26, although still coughing and expectorating, she

was feeling in good general condition and the signs of fluid in the chest had entirely disappeared. The subcrepitant rales over the entire lower lobe still persisted.

Sputum examination was negative for tubercle bacilli. Culture (Dr. Avery) showed the original smear crowded with influenza bacilli, with a few pneumococci type IV. After passage through a mouse the influenza bacilli were still in very large quantities, with also a few pneumococci type IV.

Roentgen-ray examination showed a dense shadow at the left base, homogeneous in character, due to fluid, with slight increase of the pulmonary markings above the level of the fluid. There is a large calcified tubercle at the root of the right lung.

SUBACUTE TYPE WITH RECURRENCES.

CASE X.—R. C., female, aged sixty years; first seen for this condition November 15, 1915.

Previous History. The patient has been under my observation for ten years suffering from arteriosclerosis and valvular heart disease.

Present History. November 13, 1915, she had coryza with slight fever. November 15 she was not feeling very sick and not confined entirely to bed. Her temperature was 99° and she complained of considerable spasmodic cough and expectoration.

The patient gave a history of having had a similar attack to the present one in April, 1915, while South, which lasted about a week. Communication with the physician in charge showed that he had made a diagnosis of a slight pneumonia in the right lower lobe which quickly cleared up.

Physical Examination. In the right lower lobe there was marked dulness, diminished breath sounds, and numerous moist rales.

Course of the Disease. For three days the temperature ran between 99° and 101° with continuation of the symptoms and very little constitutional symptoms. On November 17 there was a hemoptysis, about 1 dram. In five days the temperature was normal and remained so. December 20 the lungs were entirely clear.

The patient kept in ordinary health, with no signs in the chest until November, 1916, when she came in complaining of cough and expectoration which had begun two weeks previously, with no constitutional symptoms. There were a few rales at the right base. The patient took a long automobile ride and on returning home had fever to 101° and marked increase of cough and thick, purulent expectoration. The signs at the right lower lobe were much more marked. The temperature subsided in three days; the cough and expectoration disappeared in a week. When the patient was last seen December 21, 1916, there were a few fine rales at the right base.

Sputum culture (Dr. Avery) in the first attack, November 16, 1915, showed a pneumococcus type IV in almost pure culture. In the second attack, December 8, 1916, it showed pneumococcus type II B in marked predominance with almost no other organisms.

Roentgen-ray examination was not made.

CASE XI.—Mrs. C. D., aged thirty-four years; first seen March 11, 1916.

Previous History. Three years ago she had la grippe and bronchitis. In November, 1915, the patient had pneumonia which came on gradually with malaise for three days before going to bed. She had cough and expectoration and fever which lasted for about a week. She was in bed for three weeks. A report from her physician states that there was then consolidation of the entire left lung, which cleared up in the upper lobe but not entirely in the lower. When he last saw her, December 11, there were still signs in the left lower lobe similar to those present when she first came for examination, March 11, 1916.

Present History. Since the attack of pneumonia she has had considerable cough, which is worse at some times than at others. For the past month following a cold in the head this has been particularly bad. There has been no pain. The patient is three months' pregnant and consequently rather miserable.

Physical Examination. There is dulness over the left lower lobe, bronchovesicular breathing, and very moist consonating rales. The heart shows definite signs of mitral stenosis and aortic insufficiency.

Course of the Disease. The patient was put at rest and the termination of pregnancy was seriously considered. March 27, however, when last seen, she was very markedly improved and the signs in the chest were very much less. The pregnancy was allowed to go on. She has not been seen since.

Sputum Examination. Several examinations of sputum were negative for tubercle bacilli.

Culture (Dr. Avery) showed influenza in marked predominance in all of three separate specimens.

Puncture of the lung showed no growth.

Roentgen-ray examination, March 17, 1916, showed very slight increased density in the left lower lobe, peribronchial in character.

CASE XII.—J. S., female, aged thirty years; first seen September 28, 1915.

Previous History. The patient had pneumonia four years ago, reported by the physician in attendance to have been in the left lower lobe. She made a good recovery and was never very ill. Otherwise she had always been well and strong.

Present History. Eight days previously she had a gradual onset of cough and expectoration, slight fever, 100° to 101°, no pain. She had not been confined to bed and had very few constitutional symptoms. Her chief complaints were marked cough and expec-

toration. A diagnosis of acute pulmonary tuberculosis had been made.

Physical Examination. There was distinct dulness over the entire left lower lobe, some diminished respiratory murmur, and numerous rather large moist rales.

Course of the Disease. She was put to bed and kept there for two weeks. The symptoms gradually subsided. She was next seen October 29, 1915. The cough and expectoration had then entirely disappeared. The physical signs showed very few subcrepitant rales in the lower left axilla and extreme left base. December 1, 1915, examination of the chest showed it entirely normal, and since that time the patient has been perfectly well.

Sputum examination, October 1, 1915, showed pneumococci type IV markedly predominant with a few Staphylococci aureus.

Roentgen-ray examination, October 29, 1915, showed no abnormalities excepting slight increase in hilus shadows.

CASE XIII.—L. C., male, aged thirty-two; first seen March 22, 1916.

Previous History. The patient had always been well until one year previously when he began to cough, with some expectoration, especially in the morning; he had had slight malaise with some fever; he had been working regularly.

Present History. The past week he has had exacerbation of symptoms, with marked increase of cough and expectoration, and a diagnosis of tuberculosis had been made.

Physical Examination. Below the angle of the right scapula, to the base, there was a slight dulness, normal vesicular breathing, and numerous subcrepitant rales.

Course of the Disease. March 28 the symptoms were somewhat less marked, but the signs persisted as before. He was next seen April 21, 1917. He stated that he had been perfectly well until October, 1916, when he developed a cold in the head followed by marked cough and expectoration, which continued until February, 1917. His general condition was perfectly good and he continued at work regularly. Since February there has been no cough or expectoration. There were no signs in the chest in April, 1917.

Sputum culture, March 22, 1916, (Dr. Avery) showed influenza in enormous numbers in pure culture.

Lung puncture showed no growth.

Roentgen-ray Examination, March 22, 1916, showed nothing abnormal.

CASE XIV.—R. McC., male, aged fourteen years; first seen in July, 1914.

Present History. The boy had a cough which had lasted three months. He was an athlete accustomed to hard physical exercise which he had continued to take. The expectoration had recently

gotten less, but there was still a good deal of cough. There was no definite interference with the general health.

Physical Examination. In the left lower lobe posteriorly there was dulness, diminished vesicular breathing, and fine subcrepitant rales most marked on coughing.

Course of the Disease. The patient was made to rest in the country and his cough gradually improved; after four months it had almost disappeared. The signs also improved, but a few rales still persisted.

Two months later he caught a fresh cold and for a couple of days had a little fever, with marked increase of cough and expectoration. During this time the rales appeared even more numerous than when first seen. They gradually diminished after three or four weeks, but never entirely disappeared. He was taken out of regular school and sent to California, where he spent a year in the open air, during which time he was perfectly well. When he returned to New York the signs in his chest were limited to very few rales just below the angle of the left scapula. The next winter, while at his home in the country, he had another fresh cold, with recurrence of cough and expectoration and return of the rales over the same area of the chest. These persisted three or four weeks and then gradually disappeared. During the past two years the boy has been in excellent physical condition, has had no colds or cough, and on last examination there were no signs heard in the chest.

Sputum examinations were always negative for tubercle bacilli. Culture (Dr. Avery) showed pneumococcus type IV in marked predominance in two separate exacerbations.

Roentgen-ray examination, July 13, 1916, showed nothing abnormal. December 15, 1916, showed nothing abnormal.

CASE XV.—L. C., female, aged thirty-five years; first seen December 3, 1915.

Previous History. Eight years ago the patient was run down and had a slight cough. A diagnosis of tuberculosis was made. She was under a physician's care for four years, never very sick. She was told that the trouble was in the lower part of the right lung. Since then she has had occasional wheezing in the chest, but no other symptoms until the present attack.

Present History. Two weeks ago she began to cough, with a moderate amount of thick yellow expectoration. She had occasional slight fever, no pain, no night-sweats. She kept at work as a stenographer.

Physical Examination. Over the entire right lower lobe there is slightly impaired resonance, slightly diminished breath sounds, with numerous subcrepitant rales, heard especially on coughing.

Course of the Disease. She stopped work and was kept under observation. The signs gradually diminished until in a month they had almost entirely disappeared. March 10, 1916, she returned

for examination, with a history of having been perfectly well, without cough until one week previously, when she had a coryza and a return of cough, expectoration, and slight fever, about 100°. She had kept at work. Examination showed a few rales at the right base, numerous moist and consonating rales over the left lower lobe, with slight dulness.

N. B.—This is the only case in which the recurrence appeared in the opposite side from the original lesion.

Sputum examinations were persistently negative for tubercle bacilli. Culture showed pneumococci type IV predominating and a few Staphylococci mucosus.

Roentgen-ray examination, December 3, 1915, showed thickening at the roots of both lungs with enlarged bronchial glands. No abnormalities in the parenchyma and absolutely no increased shadows at the right base.

CHRONIC TYPE.

Case XVI.—Y. S., female, aged thirty-three years; first seen May 27, 1914.

Previous History. The patient had always been perfectly well until two years ago, when she gradually developed a cough and pain in the left posterior chest. At that time a diagnosis of tuberculosis was made. The patient went to the country for a few months and the symptoms entirely subsided.

Present History. A few months ago she began to have pain again in the left chest posteriorly and slight cough. She was in good general condition and was seven months pregnant.

Physical examination showed slight dulness, normal breath sounds and fine subcrepitant rales from one inch above the angle of the left scapula to the base.

Course of the Disease. The patient went to the country for a few weeks and improved a good deal. She went through her confinement normally and was next seen November 14, 1914. She was complaining of a return of a slight cough and expectoration, which at times was bloody. She was at that time nursing her child. The physical examination revealed the same signs as previously. She was advised to stop nursing and take more rest. She improved and lost her cough and kept in good health in every way, until April, 1916, when she returned again complaining of pain in her left chest but no cough. The physical signs were exactly the same as before. She was advised to give up some of her hard housework at home. She stayed in New York and kept in very good condition in every way, and had no symptoms at all until January, 1917, when she began to cough and expectorate. She had no fever and felt generally very well. The cough subsided in a few weeks, but a very marked, thick, purulent expectoration continued and the pain

in the left scapular region returned. She continued to work hard at her housework at home. She again reported for examination on April 19, 1917, when the physical signs were found to be the same as before excepting that the rales extended a little farther upward than previously.

Sputum examination was negative for tubercle bacilli on several examinations both in 1914 and 1916.

Culture, April 19, 1917, showed pneumococci type IV predominating with few Staphylococci aureus.

Roentgen-ray examination, April 23, 1917, showed slight increased density of the pulmonary markings in both lower lobes.

CASE XVII.—R. S., female, aged forty-two years; first seen June 30, 1910.

Previous History. The patient gave a history of pain in the left side, with cough and expectoration sometimes streaked with blood, three years previously. After several months a diagnosis of pulmonary tuberculosis was made and the patient spent nearly a year at Stony Wold Sanatorium.

Present History. At the time she came for examination she still had a little cough, no expectoration. She felt rather weak, although her weight and general nutrition were normal.

Physical Examination. There was a slight dulness; normal breath sounds, numerous moist rales from the angle of the left scapula to the base.

Course of the Disease. She was observed for about three months, during which time she had no fever; she felt rather weak and complained of pains in the left chest. There was very little cough. She then went to a sanatorium at Bedford Station, where she stayed about four months. She gained weight and her general condition improved. She was next seen March 16, 1911, when the physical signs were the same as before. Since that time she has been seen at regular intervals, and on every occasion the physical signs have persisted as at first. At times there would be a little exacerbation of the symptoms, with slight cough and occasional slight fever, 99° to 100°. The pain in her left shoulder-blade has always been a marked symptom. During this time her general condition has failed somewhat, and when last examined, April 19, 1917, she felt weak and dragged out, had considerable pain in her left shoulder-blade and very slight morning expectoration. The physical signs remained the same as before. Her weight is only a few pounds less than when first seen in 1910.

Sputum examination for tubercle bacilli were made frequently during all these years, and always with negative results. Culture (Dr. Avery) March 15, 1916, showed pneumococcus type IV predominating. Culture April 20, 1917, showed pneumococcus type IV markedly predominating.

Lung puncture at that time showed no growth.

Tuberculosis complement-fixation test was negative.

Roentgen-ray examination (Dr. Hirsch), April 20, 1917, showed diffuse intensification of lung markings throughout both lungs. The left diaphragm was high and irregular as by adhesions.

CASE XVIII.—P. L., female, aged thirty-five years; first seen November 19, 1913.

Previous History. Had always been well.

Present History. Nine months previously she contracted a cold in the head and cough. The cough had persisted ever since, worse at some times than at others. She thought she had had slight fever at times, but had kept at work regularly.

Physical examination showed localized subcrepitant rales below the angle of the left scapula. No abnormalities on percussion and no breath sounds.

Course of the Disease. The patient has been kept constantly under observation since that time. She has had recurrent exacerbations, sometimes with coryza and always with increased cough and expectoration. The signs have usually been slight. In March, 1914, there was a more acute attack with dulness, diminished breath sounds and very numerous moist rales over the entire lower lobe. No fever. One month later the signs had returned to their former extent.

Examination on January 1, 1915, showed the chest almost entirely clear.

She was seen on December 18, 1916. She had been very well, working regularly and was in good physical condition. Has had a few coughs and colds off and on. For the past few days she had a slight increase of cough and wheezing in the chest. On examination the rales over the left lower lobe were present over a small area below the angle of the scapula. When last seen January 19, 1917, these signs were distinctly less.

Sputum examinations for tubercle bacilli were always negative. Culture, March 25, 1914, during a more acute attack, showed pneumococcus type IV predominating; few streptococci. Culture, December 18, 1916 (Dr. Avery) showed influenza markedly predominating.

Roentgen-ray examination was not made.

CASE XIX.—Mrs. H. K., aged thirty years; first seen November 8, 1917.

Previous History. Pneumonia at fourteen, pleurisy several times, always on the right side. The last attack was one year ago. She had always been subject to colds and cough but her general health had never been affected.

Present Illness. On September 18, 1916, she had a bad cold in the head which was soon followed by marked cough and expectoration. Temperature was 99° to 100.5°. Since that time she has continued to cough and expectorate, but has had no fever. She is now six weeks pregnant, and had been told that she had tuberculosis.

Physical examination showed slight dulness, diminished breath sounds, with numerous moist rales over the entire right lower lobe.

Course of the Disease. It was recommended that the uterus be emptied and that the patient go to the country and rest. This was done. The patient returned with very much less cough and expectoration. When she was next seen on December 15 she was very much improved but still had a cough and expectoration which was occasionally blood-streaked. The signs in the chest had not changed.

The patient has been seen off and on ever since and has been doing extremely well so far as symptoms are concerned. When she was last seen March 17, 1917, she had no cough or expectoration for several weeks; the signs in the right lower lobe persisted but were distinctly less marked.

Sputum examinations were persistently negative for tubercle bacilli. Culture, November 9, 1916 (Dr. Avery) showed influenza predominating with few Streptococci hemolyticus, and few pneumococci type IV.

Roentgen-ray examination December 15, 1916, showed increased densities in both lower lobes, particularly on the right side where the clouding was rather diffuse, suggesting pleural thickening.

CASE XX.—H. F., male, aged forty-one years; first seen September 18, 1914.

Previous History. The patient had pneumonia nineteen years ago. Since that time he has been rather subject to colds and coughs but in good general condition.

Present History. Two years ago he was examined by a specialist in Montreal and told that he had tuberculosis in the lower lobe of the left lung. He rested for a month. Since that time he has been working regularly. He has had some pain in the left side which has been a little more marked of late, for which symptom he came for examination.

Physical Examination. Over the entire left lower lobe there was a slight dulness, diminished vesicular breathing and numerous fine, subcrepitant rales intensified by coughing. The patient was in good physical condition, had a normal weight, no fever or other constitutional symptoms; no cough or expectoration.

Course of the Disease. The patient has been under periodic observation up to the present time at intervals varying from six months to a year. He has had a slight cough and expectoration without coryza or constitutional symptoms, associated with dull pain in the left axilla. Physical signs have persisted throughout. During the exacerbations rales are more numerous and more moist. In the intervals they do not disappear but become distinctly less marked. The patient has kept at hard work regularly and is in excellent physical condition at the present time.

Sputum examinations have been negative for tubercle bacilli on numerous occasions.

July 19, 1916, during an acute exacerbation, cultures showed Streptococcus viridans predominating.

Roentgen-ray examination, October 25, 1915, was normal. No abnormal shadows over the left lobe. Slight increase of the hilus shadows. No abnormalities in the parenchyma of the lung.

January 15, 1917, roentgen-ray showed increase of the root shadows with a number of calcareous tubercles at the left root. Pulmonary markings somewhat intensified in both lower lobes, less marked on the left side than on the right.

Case XXI.—E. F., female, aged fifty-three years; first seen November 12, 1915.

Previous History. Double pneumonia at twenty-one when she was very ill, the onset being sudden with a chill and the attack coming on as a complication with measles. Fourteen years later she had the grippe with signs in both lower lobes and a diagnosis of pneumonia was made. She was sick five weeks with only a moderate amount of fever. The cough lasted a month longer. Seven years ago she had a recurrence of the cough with expectoration with slight fever for a few days, the cough lasting for six weeks with very little constitutional disturbance. Three years ago she had an attack similar to the last which lasted about three weeks.

Present illness began two months before the patient was first seen with cough and expectoration. She kept at work for a month. She gradually developed a slight temperature, 100° to 101°. She went to bed and the fever subsided in a week. The cough and expectoration continued but gradually improved. A diagnosis of active tuberculosis had been made.

Physical Examination. Over both lobes, particularly on the left side, there was slight dulness and very numerous and very moist rales; no changes in breath sounds. The patient at that time had no fever and was feeling very well.

Course of the Disease. She continued to improve and on November 12, 1915, the signs had almost disappeared on the right side, and were markedly diminished although still present in the left lower lobe. The patient then went South and was next seen June 2, 1916. She had had no coughs or colds or expectoration and was feeling very well. Examination showed a few rales below the angle of the right scapula and a very slight dulness over the entire lower left lobe.

Sputum examination November 13, 1915, showed pneumococci type IV in almost pure culture.

Roentgen-ray examination June 2, 1916, showed marked increase of vascular markings throughout both lungs, more marked on the right side. At the right base there was irregularity of the diaphragm, apparently due to adhesions.

Case XXII.—Mrs. W. C., aged forty-five years; first seen April 21, 1915.

Previous History. For several years she has been subject to bronchial colds and cough, at varying intervals during which time she occasionally felt a little bit feverish, but had no marked disturbance of general health. During the past winter these symptoms have been particularly marked.

Present History. For the past two weeks the patient has had the grippe with slight fever and marked increase of cough and expectoration. She had been treated for pulmonary tuberculosis and her illness was considered as such·by me for several months.

Physical Examination. Distinct dulness, diminished breath sounds, numerous moist rales over the entire left lower lobe, few pleuritic sounds over the left axilla.

Course of the Disease. The patient has been under continuous observation since that time. At times she has had practically no symptoms, but the signs in the chest have never changed and at various times there has been a little fever with an increase of cough and expectoration which has sometimes been bloody, and there has been recurrent dull pain in the left side.

Sputum examinations have been persistently negative for tubercle bacilli. Culture, November 9, 1916, showed Streptococcus viridans predominating with few Staphylococci aureus.

Roentgen-ray examination January 14, 1916, showed slight increased density in the left lower lobe. The heart was slightly displaced toward the left.

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REACTIONS TO ALTITUDE IN THE TUBERCULOUS.

By DAVID C. TWICHELL, M.D.,

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C. THEODORE WILLIAMS, of London, for forty years head of the Brompton Road Hospital for Consumptives, said in 1903, in Philadelphia, at the International Conference on Tuberculosis: "Of all my statistics of consumptive patients the high altitude cases yielded the most favorable results, and, what is most important, the fewest relapses."

My opportunities for observations on the tuberculous have been obtained by ten years' work at Saranac Lake, N. Y. (altitude 1700 feet), one year in Lower California (near sea level), one year at Silver City, N. M. (altitude 6000 feet), two years at Albuquerque, N. M. (altitude 5000 feet). Most of my training in tuberculosis has been in the school that discounts the value of altitude in the treatment of this disease.

The following is a brief summary of the changes that take place in the blood, blood-pressure, and tuberculous symptoms upon removal from a low to a high altitude.

INCREASE OF RED BLOOD CELLS. All investigators who have worked along these lines are agreed that the red corpuscles are increased by a high altitude. Zuntz showed that the activity of the red bone marrow, as shown by its hyperemia and increased number of nucleated red cells, was accelerated by low barometric pressure.[1]

The findings of the Anglo-American Expedition to Pike's Peak showed evidence that this increase was actual and not relative. The work of Wenzirl at the University of New Mexico, at Albuquerque, demonstrated that this increase of red cells was very probably only temporary. The period of abnormal increase varying in different individuals.[2]

INCREASE OF HEMOGLOBIN CONTENT. It is an established fact, I believe, that high altitudes raise the hemoglobin content of the blood.

INCREASE OF MONONUCLEAR LYMPHOCYTES. To Gerald B. Webb, of Colorado Springs, belongs the credit of the pioneer work along these lines.[3] A control experiment carried on in New York City under Dr. Hastings, at the Cornell Medical School, and under Rosenberg, in Colorado Springs, gave the following conclusion: "It is safe to assert that at an elevation of 6000 feet the large lymphocytes are absolutely increased in the circulating blood by at least 20 to 30 per cent."

INCREASE OF BLOOD PLATELETS. Gerald B. Webb has demonstrated an increase of platelets in altitude. The function of the platelets is not clearly understood as yet. My personal observations have not covered this line of work.

MODIFICATION OF BLOOD-PRESSURE. There is a wide difference of opinion on this subject. A number of observers at altitudes have noted an increase; others that the readings are the same as at sea level; and others that the pressure is lowered. This variance is in part due, in my judgment, to our unstable knowledge on the

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[1] Hohenklima und Bergwanderungen, 1906. (Review of same by Sewall, Int. Clin., 1906, vol. iv, 16th ser.)

[2] Weinzirl and Magnussen: Further Observations on Increase of Blood Counts Due to Altitude, Jour. Am. Med. Assn., May 2, 1913.

[3] Webb and Williams: Some Hematological Studies in Tuberculosis, Tr. Nat. Tuber. Assn., Fifth Annual Meeting.

whole subject of blood-pressure and to imperfect and varying technic. It is a fact that the insurance companies make no allowance for any possible variation in blood-pressure due to altitude in their examinations. My conviction from my own observations is that very probably there is a temporary change of blood-pressure which more or less corresponds with the blood changes.

Tuberculous Symptoms. In clinical observations the incidence of cough, expectoration, and fever are not strikingly altered by residence at altitude in my judgment. As to the gain and loss of weight, my observations would point to a marked difference in treatment at low and high, dry altitude. At sea level and low altitudes under the routine of rest and full diet, as a general rule, we look for marked gain in weight in all stages of the disease in which the prognosis is favorable. My observations at Albuquerque, with its low humidity and altitude of 5000 feet, point to the fact that cases in the earlier stages of the disease and in the moderately advanced stages respond by a large gain of weight under the routine of rest and full diet quite similar to such cases at low altitudes. On the other hand, advanced, semichronic and chronic cases are liable, in my experience, to lose weight or not gain weight, or gain very slowly, on coming into an altitude, especially in the dryest seasons, in the face of clinical evidence of improvement in symptoms, signs, and general well-being.

NIGHT-SWEATS. In high and dry altitude this symptom is of very rare occurrence, except for the first few nights after coming to an altitude. Even in cases that have suffered from night-sweats for a long period this symptom ceases abruptly on coming to an altitude without medication of any kind. Even in terminal collapse, night-sweats are comparatively rare or slight in altitude.

HEMORRHAGES. Hemorrhages from the lungs, in my experience, contrary to preconceived ideas, would seem to be rarer at altitudes than at lower levels.

PLEURISY WITH EFFUSION. Pleurisy with effusion is of more rare occurrence in altitudes than at lower levels.

TUBERCLE BACILLI IN THE SPUTUM. It is claimed that tubercle bacilli are more promptly lost from the sputum in altitudes than at lower levels. A control experiment by the writer is the only definite data to which I have access. The percentage of loss of tubercle bacilli from the sputum at the Trudeau Sanatorium for a year in the case of 200 patients was 7 per cent. Trudeau has an altitude of 1700 feet and high humidity record. The percentage of loss of tubercle bacilli from the sputum at the New Mexico Cottage Sanatorium at Silver City for a year in the case of 78 patients was 10 per cent. These figures should be read in the light of the fact also that the Trudeau institution has a large percentage of early cases, while the type of cases at the New Mexico Cottage Sanatorium is largely advanced and far advanced. Silver City has an altitude of 6000 feet and low humidity record.

A theoretical consideration of the phenomena observed in blood changes on coming to an altitude may be discussed, in my judgment, on the basis of a general circulatory change due to the lowered atmospheric pressure encountered. My conviction is that the circulatory mechanism permanently works to better advantage at altitudes of moderate degree, say 5000 to 6000 feet, than at sea level. It may be that the lowered atmospheric pressure at first causes a disproportionate dilatation of the venous and arterial systems, and so increasing the capacity of the blood cavities of the body. The blood-forming organs would respond to such an increased capacity as they would to loss of blood by increasing the elements of the blood. When the tone of the circulatory apparatus had been regained by adjustment to altitude the blood elements would again approximate normal. Such an increase of blood elements, if even only temporary, might be of distinct advantage in disease conditions. I believe that it is an undoubted fact that the circulation is altered in coming into an altitude. There may possibly be a temporary partial stasis of the whole venous circulation, due to anatomical reasons, that is, the thinner walls of the veins as compared with the arteries, and this possibly most marked in the pulmonary and abdominal venous circulations. This phenomenon may be of more or less degree, varying with the individual and the individual's vitality and tone. Such a partial venous stasis might have a distinct beneficial effect on disease lesions, following the theory and results obtained in Bier's hyperemia treatment.

Theoretically, it would seem that such a venous stasis, in the case of pulmonary disease would induce venous bleedings on coming suddenly to an altitude, and such is, I believe, the case. On the other hand, my conviction is that when adjustment to altitude has taken place the circulation works easier and to better advantage, so accounting for the comparative rareness of hemorrhage, in my observations, at altitudes of from 5000 to 6000 feet.

Parallel with this purely mechanical suggestion of an explanation of the observed phenomena of blood changes in altitude should be considered the theories offering an explanation along a different or supplementary line of reasoning.

Sewall offers the following possible explanation for the phenomena of mountain sickness: It is, he says, a metabolic disturbance, which is directly prone to effect newcomers in high altitudes, which is directly responsible for many of the phenomena, expecially of a psychic nature of this disorder. Mountain sickness is a curious symptom-complex manifested in very various degrees by people who mount comparatively suddenly to high altitudes. In Europe the disorder is said to be manifest at levels as low as 9800 feet. In America the critical level is considerably higher. The subjective symptoms are those of dyspnea, especially on exertion, and a feeling of oppression in the chest. Disgust for food and nausea leading to

vomiting give name to the disorder. The sufferer is absorbed in his own misery and the mental disturbance may proceed to temporary alienation. The skin and lips are blue, the circulation and respiration distressed, and the slightest exertion exaggerates intolerably all symptoms. The inhalation of oxygen gas relieves at once, for the time, the morbid condition. After a quiet sojourn of two or three days at the altitude provoking the sickness the body usually becomes accommodated to the new conditions, cyanosis of the skin disappears, the lips become red again, and the pulse and respiration return to about normal.

Sewall says that an important factor, if not the internal exciting factors, lies in circulatory disorder resulting in accumulation of blood in the venous system through inefficient heart action, and that the anoxemia would early depress the cardiac function. This would inevitably lead to plethora of the lungs and general venous system and provoke the clinical symptoms characterizing the disorder.[4]

The marked increase of hemoglobin in altitude might seem, as Sewall says, a paradox of nature in the provision of an excess of oxygen-carrying material in proportion to the diminution of oxygen to be carried. On the other hand, the conception is incontrovertible that the hemoglobin of the body is not only a carrier but a storehouse for oxygen, and the excess of this stored oxygen must be greater the lower the oxygen pressure in the alveolar air in order to meet the demands of muscular activity.

In recent researches carried out on the top of Pike's Peak, altitude 14,100 feet, Haldane, Henderson, Douglass and Schneider have apparently fully confirmed the view that active absorption of oxygen by the alveolar epithelium is an important, if not the only, force behind its appropriation by the blood when the CO_2 tension in the alveolar air falls below a certain critical tension.

It has been shown by Zuntz and others that the suboxidation of the tissues resulting from a critical lowering of alveolar oxygen tension is accompanied by the accumulation of acid substances in the blood, especially of lactic acid. These acid substances in the blood stimulate the respiratory center and lower its "threshold of irritability" for CO_2, so that the center is excited to work under the stimulus of a lower tension of CO_2 in the blood than would normally be effective.

All the above-cited factors may play a part in the blood changes observed at altitude.

The comparative rarity of natural pleural effusions as recorded by all observers at altitude may find an explanation in the improved circulatory changes.

A consideration of the loss of weight or failure to gain weight in semichronic and chronic cases, in my observation in high, dry

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[4] Sewall: Medical Climatology, Forchheimer's Therapeusis, New York, p. 270.

altitude, as compared with the experience of such cases at lower and more humid levels, can be discussed, in my judgment, with the established fact of the practical absence of night-sweats in the tuberculous in the semi-arid regions of the Southwest. It might be added that such cases later in their course, if they obtain a good arrest and become free of the chronic toxemia of their disease, in many instances make a large gain in weight.

It may be that a high, dry altitude has the double effect of improving the circulation in the deeper tissues, so liberating the toxins in a disease focus into the circulation, preliminary to their execretion through all excretory channels; while the low humidity of the surrounding atmosphere leads to very rapid evaporation and activity of the excretory function of the skin. This very rapid and constant evaporation from the skin resulting in practically no sensible perspiration, consequently no night-sweats.

The loss of weight in certain types of cases, coincident with improvement in the pulmonary lesion and the general well-being in other respects, may be accounted for through the same mechanism. The increased excretory function of the skin in dry climates results in the greater elimination of toxins by this channel, but these toxins —known in the case of tuberculosis to be direct fat tissue destroyers —in their passage through the subcutaneous tissues may lead to a greater proportionate destruction of adipose tissue.

On the other hand, this loss in tissue may be compensated for in the body economy by the direct elimination of more toxin and easement for the intestine and kidneys in their functioning. Evidence of this is seen in the often very marked improvement in digestion in these cases.

In very far-advanced types of cases with more or less active symptoms I have observed that on coming into dry altitude this increase of toxins thrown into the circulation and their elimination with the resultant rapid loss of tissue and strength may tend to hasten a fatal issue of the disease.

It might be noted here that, in my observation, the cause of death in far-advanced cases in dry altitude is, as a general rule, an overwhelming toxemia not associated with marked general edema, as is very commonly observed at lower levels with high humidity. Rapid extreme emaciation is common in these cases.

Another aspect of the clinical observation of tuberculous cases in altitude might well be considered in this discussion.

Direct reaction to altitude as shown by clinical symptoms is observed in a large proportion of tuberculous cases on coming into an altitude. This reaction may be immediate on arrival with symptoms of increased shortness of breath, increased cough and expectoration, cyanosis more or less marked, a possible tendency to slight venous oozing of blood in hemorrhage cases, and an increase of moist sounds in the lungs. (This fact I have controlled in numer-

ous cases by the report of most careful examiners who have referred cases from lower altitudes.)

This immediate reaction usually subsides promptly in a few days. A certain proportion of cases show no such reaction at all. Roughly speaking, long-standing cases with comparatively small areas of involvement are the least apt to show this type of reaction to altitude.

A second class of reaction to altitude has come under my observation, and may occur sooner or later after coming into an altitude. It is such a reaction in the course of a chronic tuberculosis as all have observed wherever the disease is treated, but is more marked in its degree and results than I have been accustomed to observe at lower levels. The symptoms of a marked sudden toxemia are observed in this type of reaction, high fever, rapid pulse, complaints of nervousness associated with insomnia, and even at times a cerebral irritation, leading to a tentative diagnosis of threatened meningitis, attacks of diarrhea, and signs of increased inflammation in the lungs. These reactions simulate closely a real relapse in the disease, and are often so designated.

The recovery from these reactions is usually a quite rapid subsidence of symptoms, as is seen in the case of the classical tuberculin reaction. They are frequently followed by periods of marked improvement in the signs and symptoms of disease, as is also observed after artificial tuberculin reactions.

In a rarefied atmosphere the muscles of the chest and neck tend to work harder. Blood and lymph tend to flow more freely in these parts. It is conceivable under these circumstances that the sweep of blood and lymph around lesions in the lungs may tend to wash out the bacterial products into the general circulation, producing the symptoms observed, with possibly some antibody formation in the process, and to be followed by the elimination of these toxins through the usual channels.

Altitude has an undoubted effect on the circulation and on the quantity and quality of the blood. Low humidity has a stimulative effect on the excretory function of the skin. Sunshine has been demonstrated to have a healing effect on certain tuberculous lesions when its rays are allowed to strike the naked body direct. These rays act powerfully in the rarefied air of altitudes and due to the coincident low humidity prevailing in the Southwest do not tend to induce debilitation in the human organism, as observed by Woodruff in the tropics, where great humidity combines with heat under excessive insolation.[5]

It would seem reasonable to see in this combination of facts some definite scientific basis for the time-honored faith in the superior healing and curative effect of altitudes in the treatment of tuberculosis.

[5] Woodruff: The Effect of Tropical Life on White Men, Med. Rec., New York, 1905, lviii, 1005.

PAROXYSMAL TACHYCARDIA IN CHILDREN.

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SIMPLE paroxysmal tachycardia occurring in children below the age of ten years is admittedly rare, especially if unaccompanied by valvular lesions of the heart. The cases which form the basis of this communication are few, but they have the virtue of being among the youngest cases thus far reported, and for this reason are most instructive. In Case 1 at least there is a clue as to the possible origin or causal factor of this condition. In these children not only is the picture of the disease fully developed, but the cases show many points of approach to adult cases, at the same time points of difference which make them studies of great interest. Lewis in 45 cases of tachycardia, accompanied or unaccompanied by cardiac lesions, either of valves, muscles, or arteries, mentions only one case below ten years of age, that of a child aged six years. He states the actual age limits as six to seventy-five years, the highest incidence twenty to thirty years, the disease occurring more frequently in the male sex. I will not enter here into the general history of paroxysmal tachycardia, which is founded upon the phenomenon as seen in the adult; such does not interest us now. There is no communication, excepting isolated cases, in the literature on this condition as it occurs in children. I am inclined to the belief that the condition is not so rare among children as we would be led to believe from the fact of its dearth of a literature. The new instruments of precision in the study of cardiac disease must in the future bring to light new cases which will give us a more definite idea of its frequency and other facts which are now unobtainable. My own cases came to me quite accidentally in the course of an uncommonly large cardiac material, and I have been aided in fixing the authenticity of the clinical diagnoses by means of cardiogram tracings, some of which accompany this paper. All these tracings were made in the cardiogram laboratory of the Mount Sinai Hospital, under the direction of Dr. B. S. Oppenheimer. The first case, which is the youngest on record, is clinically of great interest, inasmuch as the child came to me with a history that two weeks before I saw him he had suffered from an angina of some duration; he had not made a prompt recovery, but had suddenly, after a tedious convalescence, passed into the condition which I will describe.

CASE I (October 21, 1915).—A. A., male, aged twenty-two months; an only child; father and mother healthy young people;

mother had no miscarriages; normal delivery; fed on the breast for eleven months. When an infant had laryngismus stridulus; two weeks before the present illness he was ill with angina and bronchitis; when brought to me had been in this state for a day or more. He was much cyanosed and there was a general edema over the surface of the body; there was great dyspnea; the patient lay curled up on his side, which was the only position in which he could catch his breath with comfort. The examination of the lungs showed dulness and increased vocal resonance over the lower lobe behind on the right side. The liver was felt enlarged and soft some distance below the free border of the ribs; the spleen was much enlarged; the pulse could not be counted at the wrist, but over the apex varied from 224 to 280; the dyspnea was great. The case acted on the first visit in the manner seen in sudden cardiac failure in infectious diseases, such as in pneumonia in children or complicating diphtheria. The prognosis was placed seriously, and his physician advised to administer digipuratum intravenously. After a few days the heart quieted down, became slower, and in four weeks not a trace of the above attack was left. It seemed as though the boy had been saved by the prompt treatment. Two months after the attack the father noticed that the patient had spells of "cardiac irregularity" or palpitation, and with the coöperation of his physician (Dr. Doughty) I took him into my hospital service for future study. The subsequent history is best told by the hospital entries:

January 30, 1916. *Physical Examination.*

General condition: Child, very well nourished; color good.

Head: Frontal and parietal bosses.

Eyes, ears, nose: Negative.

Mouth: Tonsils enlarged but not inflamed. Throat and tongue clear.

Neck: No rigidity.

Glands: No adenopathy.

Chest: Moderate beading of ribs and Harrison's groove. When child cries there is marked inspiratory recession of the lower sternum and xiphoid.

Lungs: Clear.

Heart: Not enlarged; sounds of good force and quality. No murmurs.

Pulse: Equal; regular; good volume; tension.

Abdomen: Relaxed.

Liver: Edge felt one finger-breadth below ribs.

Spleen: Not felt.

Genitals: Negative.

Extremities: Knee-jerks.

Synopsis: Frontoparietal bosses; beading of ribs; Harrison's groove; depression of lower sternum.

February 2. This morning patient in a quiet condition after

a slight crying spell; has pulse rate of 288. Slight edema of eyelids. While in an apparently quiet condition and playing, 240. A third count makes it 270. Slight edema of surface. No enlargement of liver. No cyanosis. In a second crying spell the pulse was 126.

12.30. Crying. Heart rate 104; slowing especially on strong inspiration.

February 3. Electrical galvanic test: AO and AC greater than KO and KC. AC and AO at $1\frac{1}{2}$ milliampères. Tetanus with AO and AC of $3\frac{1}{2}$ milliampères.

February 3. Electrocardiograms are normal in an interval of tachycardia.

February 4. During a crying spell pulse rate was 132 per minute. Apex in sixth space 6 cm. from median line. Right ventricle 2 cm. from median line. No dulness behind sternum. Heart sounds normal.

February 1. Urinalysis: Acid; microscopically, negative.

February 2. Acid, 1030; microscopically, negative.

February 5. Roentgen-ray report: roentgen examination of the chest does not show any definite evidence of an enlarged thymus. The heart is approximately normal in size and shape.

The patient was readmitted to my hospital service February 1, 1917, for further study, with the history that until October, 1916, he had been quite well, of course, under the care of his physician, who under my direction had given him digitalis. The drug was not well borne, however, the pulse being depressed at one time below 60 per minute. Since October the patient had had five attacks of tachycardia, observed by the parents. At these times they had learned to know of the attacks, as the boy would complain of feeling tired and would lie down. During the preceding summer he had no attacks. A week before readmission he had a sharp pain in the precordium during the attack, with drowsiness.

The patient was readmitted to the hospital February 1, 1917.

Physical Examination. General condition: good; well nourished; not acutely ill.

Head, face, neck, eyes, ears, and mastoids: Negative.

Mouth: Tongue moist; coated; teeth good; tonsils both enlarged.

Chest: Expansion fair and equal.

Lungs: Clear.

Heart: Normal in size and position. No murmurs or accentuations.

Pulse: Equal, regular; fair tension; normal rate.

Abdomen: Soft; rounded; generally tympanitic; ulcer; no masses; no rigidity.

Liver: Upper border, fifth rib; lower border, edge felt 3 finger-breadths below costal margin.

Spleen: Not felt.

Kidneys: Not felt.

Synopsis: Palpable liver.

February 2.   Pulse rate 270 (?); counting with stethoscope $\frac{1}{6}$ of a minute, 43 to 45 (Dr. Koplik).

Apex during attack $7\frac{1}{6}$ cm. to left of median line; right side $3\frac{1}{2}$ cm. from midline.

Liver and spleen: Not palpable.
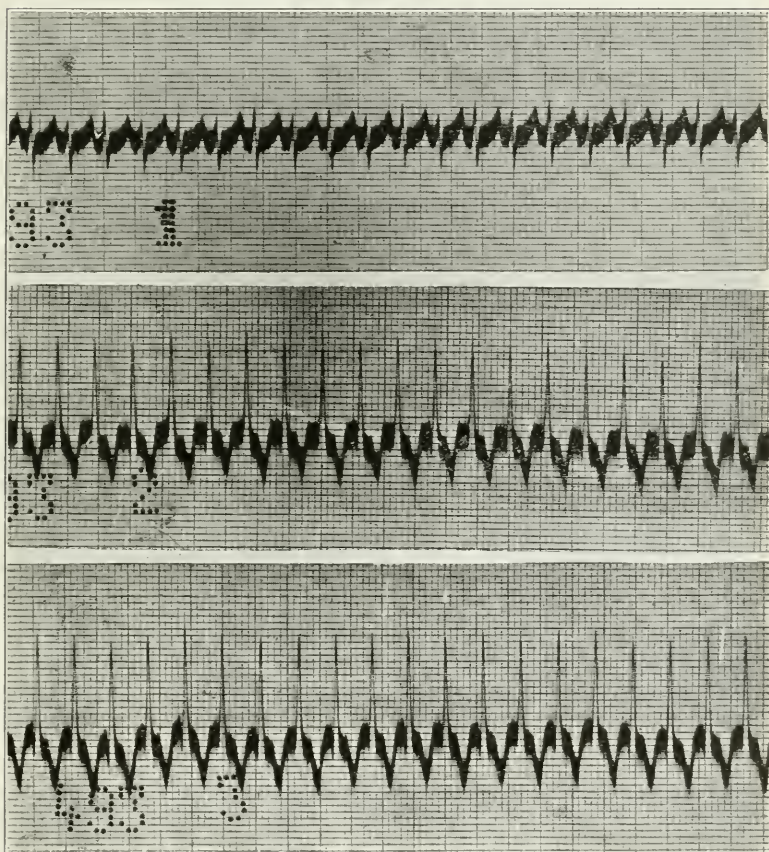
Fig. 1

Color: Normal; no cyanosis; very slight puffiness under eyes. When undisturbed there is tendency of child to lie on side.

February 3.   Pulse 168.

February 5.   Pulse 108 by auscultation; patient sitting and happy.

February 6.   Rate 96.

February 7.   Tonsils enlarged, particularly on left side.

Electrocardiogram, February 2, 1917, 493. The rate is 255 per
minute. The tachycardia is regular, of auricular origin (auric-
ular tachysystole). The R waves are small in lead I, normal
in size in leads II and III. The wave which appears to be the T
wave is upright in lead I, inverted in the other two leads. P and T
cannot be positively identified.
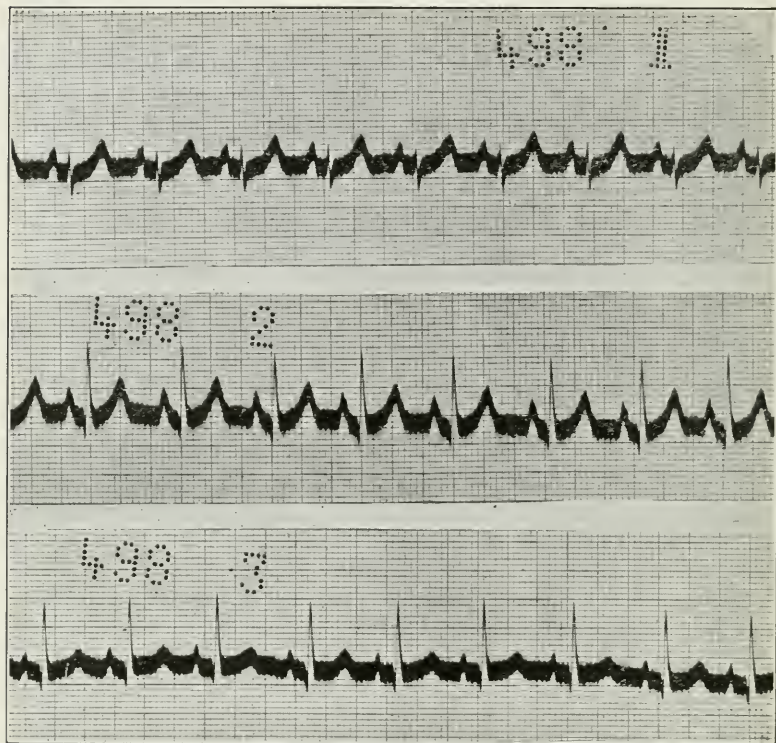
Fig. 2

Electrocardiogram, February 6, 1917, 498. The electrocardiogram
shows a return to normal rate. The T waves in lead I and II are
unusually tall and prominent. The P waves are also prominent
and slightly angular. Except for the tall T waves the electrocardio-
grams are now normal.

DISCUSSION. This case is remarkable, first having been observed
in the primary attack after an attack of the grippe, in which the
symptoms were those of an acute break-down or weakness of the
heart, with exceedingly rapid rate and signs of weakness of the
heart in edema of the general surface of the body, cyanosis, swelling
of the liver and spleen, and great dyspnea, as seen only in impending
death. An improvement and apparent cure took place, and then a

period of comparative comfort and freedom, followed by regular attacks of paroxysmal tachycardia of varying duration. One attack in the hospital lasting a few hours and another fully twenty-four hours. The spleen and the liver never enlarged to the extent in the subsequent as in the first attack. The cyanosis did not reappear nor did the general edema after the first attack. During the habitual attacks or paroxysms the boy was not uncomfortable. He would at times sit and play with a rate of 204 pulse, at others would lie quietly in his crib, pale, eyelids slightly puffy, and say he felt tired. Otherwise between the attacks he impressed one as an exceedingly bright, active child of good color, with marks of early rachitis. It is possible in this case to assume that the first attack of influenza was the starting-point of his affection and that the cardiac collapse of the first attack was the forerunner of the subsequent attacks, and that in this case there was a serious involvement of the myocardium as the result of the influenza. A tachycardia was thus established on the foundation of some form of infective myocarditis.

CASE II.—The second case which I have to report came under my notice when the patient was three years old. The previous history taken in my office states that as an infant her physician, when she was six months of age, told the parents the baby had a rapidly beating heart. This was brought to their notice every few months, and the symptoms had subsided, or were not noticed again, until three months before she was seen by me. A physician again told the parents that the child's heart was weak. I then sent her to my service for study.

J. S., female, aged three years, admitted to the hospital April 21, 1916.

Family History. Father and mother living and well; one sister, six months old, well.

Past History. Normal delivery; weight at birth eight pounds. No other illness up to the present. Had tonsillitis. Has not had measles.

Present Illness. Patient has had attacks of palpitation for the past three months. The last attack still persists. Patient has no dyspnea; does not cough. No bloody expectoration. When she gets her paroxysmal attacks, patient feels like vomiting, but only does so on rare occasions. No gastro-intestinal symptoms; no urinary disturbances. Has no visual or aural disabilities. Appetite poor.

Synopsis: Palpitation occasionally for three months.

April 21: Physical examination (a few hours later).

General condition: Good. Patient fairly well nourished.

Head: Well formed.

Face: Negative.

Eyes: Negative; no petechiæ, palsies, icterus, or nystagmus.

Ears, nose, mastoids: Negative_externally. ·

Mouth: Teeth in good condition. Tongue coated and moist. Throat clear. Tonsils enlarged. No exudate.

Neck: Negative.

Chest: Well formed; expansion fair and equal.

Lungs: Anterior and posterior, negative; no dulness or rales.

Heart: Apex beat not seen or felt; no thrills or abnormal pulsations. Upper border, third rib; right border, right sternal margin; left border, two and a quarter inches from median line. Action regular; fair force; extremely rapid (240 at apex); sounds clear; no murmurs; no accentuations.

Pulse: Equal; regular; rapid.

Abdomen: Lax; tympanitic.

Liver: Upper border sixth space to one-half inch below costal border, where edge is distinctly felt.

Spleen and kidneys: Not felt.

Skin: Negative.

Glands: Negative.

Spine: Negative.

Extremities: Upper, negative. No clubbing of fingers or incurving nails.

Extremities: Lower, negative.

Synopsis: Cardiac condition.

May 8: Child in bed, quiet, smiling. Pulse rate 228.

May 8: Electrocardiogram No. 168 shows a tachycardia of approximately 250 ventricular beats per minute. The P waves (auricular) cannot be identified, but are probably combined with the T waves, probably falling on the descending limb of the wave.

Heart action is regular, the ventricular complexes during the tachycardia resembling the ventricular complexes taken on April 22, when the heart action was comparatively slow, so that one may assume that the impulses during the paroxysm of tachycardia are supraventricular in origin. It may be safely said that the tachycardia is not ventricular in origin.

May 25. Electrocardiogram taken in an interval in which there was no tachycardia shows a pulse rate of 108 beats per minute. The P wave is tall in lead I. The T wave is inverted in lead II. The P wave in lead III is well marked and upright.

May 26. The record of electrocardiogram is the same except that in lead III the P wave is so little marked as to be indistinguishable and in certain cycles is diplasic.

DISCUSSION. In this case I saw the child when the cardiac condition was well established and observed the attacks of tachycardia then. The objective symptoms were few; the child would sit up in bed and play with the heart beating at an incredible rate. The attacks were paroxysmal, and in the interval the child, though pale, was not noticeably a sick child. In an attack the child was pale and nervous, but only slightly so; irritable; no swelling of the

liver or spleen; no puffiness of the face with simply an indisposition to be disturbed. The child slept well; appetite was good; there were surprisingly few symptoms objectively and subjectively.
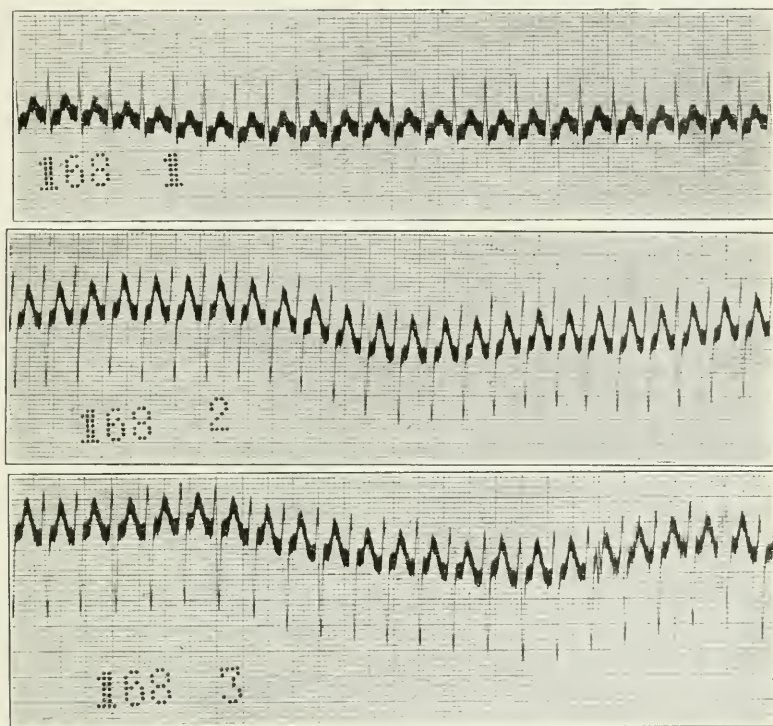
FIG. 3

CASE III.—The third case which I have to report has been under observation for two years in my service at the hospital, having been readmitted twice for his malady. He presents several features, in addition to those observed in the other cases, which I will try to bring out.

S. P., male, aged ten years, admitted June 16, 1915; discharged August 25, 1915.

Diagnosis. Paroxysmal tachycardia; auricular flutter.

Chief Complaint. Cardiac palpitation.

Family History. Father and mother are living and well. Three brothers and sisters are living and well.

Past History. Had measles; no scarlet fever; no sore throats.

Present Illness. Two months ago (?) patient had abdominal pains and vomited often. No cardiac palpitation noted at this time; child did not appear to be weak and played around. Five days ago began to vomit again, at this time cardiac palpitation was

noted and the child became very weak and was unable to walk up steps. Bowels constipated.

Examination. General condition fair; moderate cyanosis of lips and ears.

Mouth: Both tonsils contain cheesy follicles, are ulcerated, and contour irregular. Palpable externally.

Nodes: Cervical; axillaries and inguinal nodes palpable.

Skin: Scars on chest and abdomen.

Lungs: Negative.

Heart: Upper border, third rib; right border midsternal line; left border, three-quarter inches to left of midclavicular line. Apex in sixth space.

Pulse: Absolutely irregular periods of tachycardia followed by slow pulse, the beats of which are irregular.

Heart: Action is irregular; first rapid and then slow; sounds of poor quality and valvular in character. No murmurs. Apex beat 200 per minute.

Liver: Sixth rib to one finger-breadth below umbilicus. Liver is tender on palpation.

Spleen: Not felt.

Extremities: Knee-jerks present; no edema.

June 29. Heart rate slow, between 70 and 80 per minute. Action irregular in force and rhythm. No murmur heard.

July 1. Marked tachycardia. Apex rate 208. No murmurs heard. Pulse rate difficult to count, small beats being missed about 130. Observed to have continued twelve hours (morning and evening rounds).

July 2. Cardiac rate 100, irregular. Pulse rate 54, very irregular; pulse deficit 46.

Cardiac rate 104, very irregular.

July 5. Tachycardia lasting several minutes observed. Therefore observation of July 1 may indicate constant tachycardia of twelve hours' duration.

August 7. Pulse and ventricular rate equal and regular, 88 per minute. Veins in neck, however, seem to pulsate much more rapidly —too rapidly to be counted. Venous pulsation seems to be rhythmical, now that ventricular action is slow and regular.

August 9. Pulse rate 100 for two consecutive minutes. Occasional extrasystole present.

August 16. Heart action still slow and moderately irregular.

August 22. Heart action now perfectly regular, about 100 per minute.

Temperature. June 16 to August 25, 98 to 99.2, with occasional rises to 100 or 100.2.

Weight: June 21, 44 pounds 7 ounces; August 22, 50 pounds.

Urinalysis: Usually amber; acid; specific gravity varied from 1012 to 1022, on two occasions there was a faint trace of albumin,

microscopically there were white blood cells, and on June 25 there were occasional red blood cells.

Readmitted: September 24, 1915. Patient was discharged from the hospital on August 25, 1915. Felt well until yesterday morning, when he had dyspnea and had slight epigastric pain and vomited. Toward evening his heart began to beat rapidly, causing distress.

Examination: General condition fair; rather marked degree of pallor; respiration increased; somewhat dyspneic.

Eyes: Pupils equal; react to light; no petechiæ.

Mouth: Teeth in bad condition; tongue moist. Tonsils moderately enlarged, irregular in contour.

Glands: Few cervicals; axillaries and inguinal nodes palpable.

Skin: Scar over epigastric region.

Lungs: Negative.

Heart: Action slow; regular; sounds are of good quality; no murmurs; no pulse deficit: no tachycardia. (On admission heart action was very rapid, 190 beats per minute, pulse 130.)

Abdomen: Soft; lax; tympanitic; no fluid.

Liver: Upper border, fifth rib, to one finger-breadth below free costal border, where edge is indistinctly felt.

Spleen: Not felt.

Genitalia: Negative.

Extremities: Knee-jerks present; no edema.

September 8. Cardiac rate during stage of tachycardia 270 (during last few seconds heart was breaking into slow rhythm). Duration of tachycardia about two minutes, regular. Cardiac rate during slow period 104 and irregular.

September 15. Heart action slow and regular. Liver has receded in size to costal margin.

Temperature: September 24 to October 22, irregularly 98 to 100.

Urine: September 24 to October 22, usually amber; acid; specific gravity varied from 1012 to 1024; microscopically occasional white blood cells.

Laboratory Examination: September 20, Wassermann reaction negative.

Readmitted October 2, 1916.

Present Illness. Since leaving hospital two and one-half months ago patient has been at Rockaway Beach. Has had repeated attacks of cardiac palpitation, headache, and nausea, with free intervals of five days to two weeks. Present attack began fifteen days ago.

Synopsis. Since leaving hospital two and one-half months ago repeated attacks of palpitation and nausea. Present attack, fifteen days' duration.

Physical Examination.

General condition: Good. Patient comfortable, not acutely ill.

Head and neck: Negative.

Mouth: Left tonsil shows small exudate; tonsils slightly enlarged. Teeth in poor condition.

Thorax: Chest well and equally developed. Respirations free, equal.

Lungs: Resonant throughout; no rales or rubs.

Heart: Action regular; very rapid; sounds clear; no murmurs or thrills. Apex fifth space.

Pulses: Equal; regular; extremely rapid.

Liver: Upper limit sixth rib; lower border not felt below border of ribs.

Abdomen: Rounded; soft; no masses or tender points.

Spleen and kidney: Not felt.

Abdominal reflexes: Present.

Liver: Felt two inches below costal margin.

Extremities: Normal knee-jerks.

Skin and glands: Negative.

Spine and joints: Negative.

Synopsis: Cardiac condition.

October 5. The tachycardia noted on admission has subsided.

November 26. Tachycardia persists.

November 29. Tachycardia has been present for the past twenty-four hours, which is only one of a series which has been continuous for the past few days. Impossible to fix exact duration, both at base and apex. Signs of irregularity and premature contractions. Pulse at wrist small but very rapid, 216 at right radial; left radial pulse not so distinct, cannot be counted. Apex 216, 216 at base.

November 29. Tachycardial attack still present. Pulse at wrist 192. Pulsation of jugular of right and left side of neck. Slight puffiness of eyes and brownish color of face. Liver just palpable but not enlarged. Spleen enlarged. Child not uncomfortable.

December 1. Attack still persists. Irregularity present.

December 3. Tachycardial attack has ceased.

December 9. Marked tachycardia this morning.

Urinalysis. Clear; acid; 1014 to 1030; albumin occasionally, very faint trace; microscopically negative.

The electrocardiograms taken in this case are exceedingly numerous, and may be summerized as follows:

1. A condition of auricular flutter with varying degrees of heart-block 2 to 1 or 3 to 1. There were also ventricular extrasystoles arising from the right ventricle.

2. An auricular tachycardia (auricular tachysystole) which in one cardiogram showed in leads *I* and *II* that every third auricular beat was blocked and not followed by a ventricular response. In lead *III* the auricular and ventricular beats were equal, the rate of both being 225.

3. An auricular rate of at times 180 to 192 beats with ventricular rate depending on the grade of heart-block 2 to 1 or 3 to 1.

DISCUSSION. This is a case of paroxysmal tachycardia in which the paroxysms may be very short, extending in one actual instance over three minutes and in another over forty-eight hours. In those paroxysms in which the attacks are prolonged it is to be assumed that there may be short periods of rest to the heart which have been interspersed in the prolonged attack. During an attack the rhythm of the heart is very irregular at times, and there are periods of auricular flutter with heart-block. Between the attacks the rhythm of the heart may be also irregular or show periods of block even when digitalis has not been administered. The duration of the attacks has been referred to. A study of the cardiograms shows that this case is one of auricular tachycardia, as is also the first case. The second case being particularly, according to the cardiogram report, one in which the impulses, during the paroxysm of tachycardia, are supraventricular in origin. A study of the pulse respiration ratio in cases 1, 2, and 3, are given here, with the reservation that the pulse counts were made in a clinical way at the wrist or carotid by nurses in the wards, and must be thus adjudged. As one would expect, *a priori*, the respirations are increased with the pulse rate, but there is nothing objectively approaching what we would name dyspnea. The children did not present the appearance of respiratory distress at any time. To be sure, they were confined to their cribs during the attacks.

PULSE AND RESPIRATION RATIOS. CASE I.

		Respiration.	Pulse.
January	30, 1916	32	124
	31, 1916	28	128
February	1, 1916	28	120
	1, 1916	24	80
	2, 1916	28	76
	2, 1916	44	216
	2, 1916	40	136
	2, 1916	32	120
	2, 1916	28	84
	3, 1916	30	116
	3, 1916	28	96
	4, 1916	32	118
	4, 1916	30	100
	5, 1916	30	96
	5, 1916	28	118
	5, 1916	28	108
	5, 1916	24	88
	6, 1916	28	80
	6, 1916	28	128
February	1, 1917	26	108
	1, 1917	28	(?) 180
	2, 1917	26	(?) 204
	2, 1917	28	180
	3, 1917	26	128
	3, 1917	28	96
	4, 1917	26	116
	4, 1917	26	120
	5, 1917	26	108
	5, 1917	28	100
	5, 1917	26	104

PULSE AND RESPIRATION RATIOS.   CASE II.

			Respiration.	Pulse.
April	21, 1916	. . . .	28	156
	21, 1916	. . . .	36	140
	22, 1916	. . . .	36	108
	27, 1916	. . . .	26	92
May	1, 1916	. . . .	28	100
	4, 1916	. . . .	24	70
	8, 1916	. . . .	24	228
	9, 1916	. . . .	24	78
	11, 1916	. . . .	36	200
	11, 1916	. . . .	26	240
	17, 1916	. . . .	36	200
	17, 1916	. . . .	28	192
	20, 1916	. . . .	40	108
	22, 1916	. . . .	28	208
	25, 1916	. . . .	24	92
	26, 1916	. . . .	24	120
	27, 1916	. . . .	36	212
	30, 1916	. . . .	24	96
June	1, 1916	. . . .	20	92
	4, 1916	. . . .	20	80
	6, 1916	. . . .	36	92
	7, 1916	. . . .	36	250
	8, 1916	. . . .	44	205
	8, 1916	. . . .	32	160
	9, 1916	. . . .	28	112
	10, 1916	. . . .	36	200
	11, 1916	. . . .	38	248
	12, 1916	. . . .	28	100
	13, 1916	. . . .	20	88
	14, 1916	. . . .	28	110
	14, 1916	. . . .	26	84
	15, 1916	. . . .	26	84
	16, 1916	. . . .	20	104
	17, 1916	. . . .	32	128
	18, 1916	. . . .	24	100
	20, 1916	. . . .	20	84
	21, 1916	. . . .	24	96
	22, 1916	. . . .	24	120

PULSE AND RESPIRATION RATIOS.   CASE III.

			Respiration.	Pulse.
June	16 to June	22, 1915	30	160
	16 to	22, 1915	24	96
	23 to	29, 1915	24	92
	23 to	29, 1915	24	76
	30 to July	6, 1915	24	94
	30 to	6, 1915	24	80
July	7 to	13, 1915	28	96
	7 to	13, 1915	24	80
	14 to	20, 1915	24	100
	14 to	20, 1915	24	80
	21 to	27, 1915	24	102
	21 to	27, 1915	24	80
	28 to August	3, 1915	24	154
	28 to	3, 1915	24	80
August	4 to	10, 1915	24	104
	4 to	10, 1915	20	80
	11 to	17, 1915	24	96
	11 to	17, 1915	22	88
	18 to	24, 1915	28	112
	18 to	24, 1915	22	88

PULSE AND RESPIRATION RATIOS.   CASE III *(continued)*.

	Respiration.	Pulse.
September 4, 1916	34	144
10, 1916	30	136
17, 1916	28	100
24, 1916	24	96
28, 1916	24	108
October 4, 1916	24	56
15, 1916	24	88
31, 1916	24	84
November 10, 1916	24	162 (?), 176 (?)
12, 1916	24	80, 120, 110
15, 1916	24	108, 64
26, 1916	24	90
29, 1916	24	162, 196, 88
December 5, 1916	24	60
10, 1916	24	104
12, 1916	24	112
17, 1916	24	72
26, 1916	24	54
January 6, 1917	24	72, 80, 90
14, 1917	24	70
February 11, 1917	24	90
16, 1917	24	84
19, 1917	24	88
March 2, 1917	20	72
9, 1917	24	104
11, 1917	44	160
14, 1917	20	104
17, 1917	22	80
19, 1917	24	112
19, 1917	20	84
30, 1917	28	120
April 1, 1917	24	104

APRIL 5, 1917.   A PAROXYSM, TACHYCARDIA.

		Pulse.		Respiration.
2.45 P.M.	Attack started	144		32
3.00 P.M.	....	208		44
3.15 P.M.	....	196		40
3.30 P.M.	....	200		40
3.45 P.M.	....	192		38
4.00 P.M.	....	200		40
4.15 P.M.	....	204		42
4.20 P.M.	....	100	(a pause)	26
4.30 P.M.	....	180		40
5.00 P.M.	....	184		38
5.30 P.M.	....	192		40
6.00 P.M.	....	188		38
6.30 P.M.	....	180		36
7.00 P.M.	....	184		30

APRIL 8, 1917.

		Pulse.	Respiration.
10.00 A.M.	Attack started	200	40
10.30 A.M.	. . . .	180	40
11.00 A.M.	. . . .	192	38
11.30 A.M.	. . . .	196	38
12.00 M.	Pulse intermittent	188	36
12.30 P.M.	. . . .	192	36
1.00 P.M	. . . .	196	38
1.30 P.M.	. . . .	192	36
2.00 P.M	. . . .	196	36
2.30 P.M	. . . .	196	36
3.00 P.M.	. . . .	180	32
3.30 P.M.	. . . .	176	32
4.00 P.M.	. . . .	168	30
4.30 P.M	. . . .	164	28
5.00 P.M.	. . . .	164	28
5.30 P.M.	. . . .	150	28
6.00 P.M	Pulse intermittent	150	28
6.30 P.M.	. . . .	130	26
7.00 P.M.	. . . .	130	26
7.30 P.M.	Attack ceased	120	28
9.00 P.M.	. . . .	96	24
11.00 P.M.	. . . .	96	26
12.00 MID.	. . . .	100	24
12.30 A.M.	. . . .	104	24
1.00 A.M.	. . . .	104	24

Additional studies of the pulse and respiration ratios in Case III
(S. P.), showing the interpolation of short paroxysms of tachycardia
and duration of paroxysms.

APRIL 13, 1917.

Time.	Pulse. Radial.	Apex.	Nurse's notes.	Respiration.
12.30 A.M.	80	. .	Attack started; intermittent.	24
1.15 A.M.	56	. .	Irregular, of fair quality, at first feeling rapid and fluttering, and suddenly dropped to perceptible amount of 56.	24
1.35 A.M.	56	. .	. . . .	24
2.00 A.M.	?	?	Fluttering.	24
2.30 A.M.	104?	. .	. . . .	24
3.00 A.M.	80	104	. . . .	24
3.30 A.M.	92	. .	. . . .	24
4.00 A.M.	76	?	Very irregular.	24
5.00 A.M.	88	120	Radicle irregular; apex bounding.	24
5.30 A.M.	?	160	. . . .	24
6.00 A.M.	?	200	Complains of sticking pain in left axilla.	22
6.30 A.M.	?	136	Respirations abdominal and seem restrained on patient's part.	24
7.00 A.M.	?	200	. . . .	24
7.30 A.M.	?	204	. . . .	26
8.00 A.M.	?	196	. . . .	26
8.30 A.M.	?	196	. . . .	24
9.00 A.M.	?	192	. . . .	24
9.30 A.M.	?	196	. . . .	24
10.00 A.M.	?	192	. . . .	24
10.30 A.M.	?	180	. . . .	24

APRIL 13, 1917 (*continued*).

Time.	Pulse. Radial.	Apex	Nurse's notes.	Respiration.
11.00 A.M.	..	176	....	24
11.30 A.M.	?	?	....	24
12.00 NOON	..	152	....	24
1.00 P.M.	..	168	....	24
2.00 P.M.	..	168	....	24
2.30 P.M.	..	172	....	22
3.00 P.M.	.	170	....	24
4.00 P.M.	..	160	....	24
4.30 P.M.	..	164	....	22
5.00 P.M.	..	172	....	24
5.30 P.M.	..	176	Attack still on; pulse imperceptible at times; patient has headaches and complains of pain in left axilla occasionally.	24
6.00 P.M.	..	180	....	26
6.30 P.M.	..	172	....	24
7.00 P.M.	..	176	....	24
7.50 P.M.	88	88	Intermittent.	24
7.55 P.M.	128	..	....	24
8.30 P.M.	..	188	....	24
9.00 P.M.	116	..	Pulse varied, 88 to 188; respirations 24.	24
10.00 P.M.	96	..	Distinctly tricotic at 188.	24
11.00 P.M.	120	..	....	24
12.00 MID.	..	144	....	24

Pulse and respiration ratio and short momentary tachycardial paroxysms in the intervals of prolonged paroxysms.

CASE III.   APRIL 14, 1917.

Time.	Pulse. Radial.	Apex.	Nurse's notes.	Respiration.
1.00 A.M.	88	..	....	24
2.00 A.M.	..	144	....	28
3.00 A.M.	..	160	....	24
4.00 A.M.	..	120	....	24
5.00 A.M.	80	..	....	24
6.00 A.M.	136	..	....	24
7.00 A.M.	48	140	....	24
7.30 A.M.	..	188	....	24
8.00 A.M.	..	184	....	24
8.30 A.M.	..	?	....	24
9.00 A.M.	..	180	....	24
9.30 A.M.	..	172	....	24
10.00 A.M.	..	160	....	22
1.00 P.M.	..	186	....	24
1.30 P.M.	..	192	....	22
2.00 P.M.	..	200	....	26
2.30 P.M.	..	184	....	24
3.00 P.M.	..	180	....	24
4.30 P.M.	..	156	....	22
5.00 P.M.	..	160	....	22
5.30 P.M.	..	164		
6.00 P.M.	..	136	Pulse varying, 200 to 136, irregular and intermittent at times; complains of headache.	24

CASE III.   APRIL 14, 1917 (*continued*).

Time.	Pulse. Radial.	Apex.	Notes.	Respiration.
6.30 p.m.	..	136	. . . .	24
7.00 p.m.	..	156	. . . .	24
8.00 p.m.	84	..	. . . .	22
9.00 p.m.	72	..	. . . .	24
10.00 p.m.	80	..	Attack ceased.	24
11.00 p.m.	80	..	. . . .	24
12.00 mid.	80	..	. . . .	24
1.00 a.m.	80	..	April 15, 1917.	24
2.00 a.m.	80	..	. . . .	24
3.00 a.m.	84	..	Attack lasting two minutes; pulse 184; respirations 24.	24
4.00 a.m.	80	..	. . . .	24
5.00 a.m.	80	..	. . . .	24
6.00 a.m.	84	..	Attack of rapid pulse, approximately lasting thirty seconds.	24
7.00 a.m.	80	..	. . . .	24
9.00 a.m.	84	..	. . . .	22
11.00 a.m.	108	..	. . . .	22
1.00 p.m.	160	..	. . . .	22
3.00 p.m.	120	..	Attack lasting two minutes; pulse suddenly became very rapid, 204(?), then heart-block about three seconds, then 88 regular.	22
5.00 p.m.	108	..	. . . .	22
7.00 p.m.	106	..	. . . .	22
9.00 p.m.	96	..	. . . .	22
11.00 p.m.	84	..	. . . .	24

Several questions arise in connection with these cases which are of interest. The first question asked me by physicians is, What is the fate of these children? We have no records of any which have been followed from childhood to adult life. We cannot say, therefore, whether the abnormal condition of the heart innervation leads ultimately to exhaustion of the heart muscle with all the symptoms of heart weakness and ultimate death. This must remain for future observation. It may be that many of these children being attacked by some intercurrent affection die of heart weakness and never reach adult life. The opposite may be true that the heart may ultimately return to its normal innervation. Another point of interest is the management of these cases. They all seem to be perfectly comfortable, if not subjecting the heart to any excessive strain, such as muscular exertion in play or running. It would seem in this that our observations agree with a solitary case in the literature published by Hutchinson and Parkinson of tachycardia in a child, aged two years and eight months. In this case the subjective and objective symptoms were few and resembled closely those of Case I in our series. Digitalis controls but does not cure the condition; on the contrary it is difficult to prevent a digitalis heart-block if digitalis is administered, and it would seem as though the children were as well off without digitalis as with the drug. On the other hand, in a case (as

in my Case I) in which the heart threatened to collapse in the first attack of tachycardia, digitalis would seem to have saved the day. In this case the heart is now very sensitive to the use of digitalis, which, even in small doses, is apt to bring about a reduction of pulse rate with heart-block which is disagreeably alarming. So that we may infer that the heart is peculiarly sensitive in these cases to the action of the drug, which must be used in controlling ordinary attacks with extreme caution. The interval use of digitalis in these children is to be rejected. It is to be used in cases only of imminent cardiac failure and collapse.

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THE MEDICAL ASPECT OF GASTRO-ENTEROSTOMY.[1]

By Herbert S. Carter, M.D.,

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For the most part the discussion of gastro-enterostomy has been in the hands of the surgeons, who deserve unstinted praise for having placed this important operation on such a secure scientific footing by ceaseless labor and experimentation. At the same time the subject has a very pertinent medical aspect, for these cases are practically all medical before they are surgical, and they are, or should be, medical *after* they are surgical. In the discussion of the subject that follows, this operation in relation to chronic gastric or duodenal ulcer alone is under consideration.

The reason that these cases are medical before they are surgical is that they should all be given the benefit of a thorough, painstaking, medical cure before surgery is considered, or even two medical cures. This means bed for three or four weeks and the employment of some such diet as von Luebe's as originally planned, or as modified by Lockwood, or a long-continued milk, egg, and cream diet, with or without bismuth and alkalies, as in Sippy's cure. The Lenhartz diet is not to be recommended for chronic ulcer unless the diet for the first six days is used and gradually extended along more conservative lines, and not as planned by Lenhartz. The reason for insistence on one or more thorough medical "cures" is because a fair proportion of cases do get permanently well on this plan of treatment and are spared the operative risks, as is well shown by the following statistics:

[1] Read before the Medical Section of the New York Academy of Medicine.

In 1899[2] Joselin collected 114 cases of ulcer treated medically and found that 80 per cent. were cured at the end of the treatment, but after five years only 40 per cent. had remained well.

In 1914[3] he published another series of cases collected from 1899 to 1914, 131 cases in all, with the following result: Cured, 39 per cent.; improved, 42 per cent.; unimproved and died, 19 per cent. In 18 cases traced from the records of the Presbyterian Hospital a few years ago there were: Cured, 50 per cent.; improved, 12 per cent.; unimproved and died, 38 per cent. These were traced one to six years (average three and one-third years) after treatment. All these cases treated medically showed a fair degree of success, 40 per cent. for the combined series of 263 cases. Although the diagnosis of ulcer, in the nature of things, could not be confirmed, and doubtless there are included cases of chronic appendicitis or gall-bladder disease, either of which can so perfectly simulate ulcer; but even granting that half the cases are wrongly diagnosed, we still have 20 per cent. of cures or one-fifth of the cases cured by medical means alone, and it is probably actually about 30 to 50 per cent. In advising medical treatment we must take into consideration the probable location of the ulcer and age of the patient. When the patient is young and the ulcer probably duodenal there is no objection to a medical cure. If, however, the patient is in the cancer age and the ulcer seems more likely to be gastric and chronic, there should probably be no delay in advising an operation. Duodenal ulcers do not degenerate into cancer. Gastric ulcer is very apt to do so and should always be excised if possible.

NECESSITY FOR GASTRO-ENTEROSTOMY. The indications for the operation, provided a medical cure has failed or is inadvisable, are:

1. Chronicity of the symptoms in spite of medical treatment.
2. Repeated hemorrhage or very severe hemorrhage (late operation).
3. Pyloric stenosis.

Chronicity speaks for itself, in that it is safer for the patients who have failed in medical treatment to be treated surgically, but a word must be said about hemorrhage. It is a fortunate fact that very few cases die of hemorrhage no matter how alarming it may seem. The exceptions to this rule are not negligible, but are fortunately small in number, for occasionally a case does die of severe hemorrhage. The fact that so few die from hemorrhage is indeed fortunate as well from a surgical stand-point, as an operation done at the time of hemorrhage is not a favorable procedure.

If the hemorrhage has been severe it is wise to perform the gastro-enterostomy when the patient has made up sufficient blood, say after ten days or two weeks, to prevent a recurrence of what

[2] AM. JOUR. MED. SC., August, 1899.
[3] Jour. Am. Med. Assn., 1914, lxiii, 1836.

might be a fatal hemorrhage later, or if immediately necessary should be preceded by transfusion if the hemoglobin is low.

In regard to the operative indications for pyloric stenosis, almost all authorities agree that this is a definite indication for operation, although Sippy[4] positively states that he has seen almost no cases that would not yield to his form of medical treatment and diet. His results have not as yet been confirmed on a large scale by other investigators. The previous poor opinion of the operation of gastro-enterostomy in the minds of many men has been on account of the fairly numerous surgical failures which were seen years ago more frequently than now. Some of the results were far from encouraging and left the patients often cured of their ulcer, but with almost worse ills from vicious circle and digestive discomfort of all sorts.

On the other hand, following the medical case histories at the Presbyterian Hospital, it was fairly frequent that one found a case discharged as cured from the medical service entered later on the surgical records as requiring operation for one cause or another.

RESULTS OF GASTRO-ENTEROSTOMY. Immediate (up to six months postoperative). There are many questions that come to mind to which a categorical answer would be welcome, but a good many still remain to be solved, and one can only indicate in a general way some of the results on:

1. Symptoms.
2. Gastric secretory changes.
3. Gastric motility.

The immediate effect on the symptoms is usually a happy one after the postoperative discomfort is over, the patients almost always finding that they are freed from the pain and distress coming on two to four hours after meals, which these cases suffer so much from before operation.

2. The change in secretions is often insignificant, and in general it may be said that the acid values shown by gastric analysis are all somewhat lowered; but the case that was hyperacid before operation is apt to remain hyperacid to the end of the chapter, and particularly in the few weeks following operation, although the acid values are less; the cases with normal preoperative acidity are seen to have this more or less reduced, but often show little change; again, some cases promptly swing clear through to an achylia. Hypersecretion either continuous or alimentary, is regularly a part of most operations on the digestive tract, but after this postoperative effect has passed, certain cases remain with a hypersecretion, in some instances simply a continuance or increase of preoperative hypersecretion, in others occurring for the first time only after operation. Operation on a stomach with normal secretions and motility often results: (1) "In stasis or hypersecretion or both

4 Jour. Am. Med. Assn., June, 1915, p. 1625.

(particularly with an occluded pylorus), and (2) operative treatment on a stomach with delayed motility and hypersecretion usually brings motility to normal and lowers acidity."

The modification of the symptoms and secretions is undoubtedly due to:

1. The relief of the pylorospasm which follows the operation.
2. The inflowing of alkaline jejunal contents.
3. Lessened emptying time of the stomach provided the pylorus has not been occluded.

When we come to investigate gastric motility immediately after operation we find several factors at work. If the patient is generally weak and miserable there will undoubtedly be atony and delayed emptying, and this is particularly true if the pylorus has been occluded. If, on the other hand, vigor is fairly promptly restored and the pylorus is patent, so providing two ways of exit for the chyme, the gastric motility is better and the emptying time shortened to less than normal. In fact, in these cases it is often difficult to get a test meal, as the stomach empties frequently in twenty to thirty minutes. One thing must be kept in mind, namely, that practically nothing leaves through the gastro-enterostomy opening unless it is directly pushed through by the gastric muscle; the opening does not act like a bung-hole in a barrel. The presence of an accompanying gastroptosis usually aids in prolonging discomfort and emptying time as well as in keeping the acidity at a fairly high level.

Still another immediate effect noted is the change in the character of the stools which for some weeks after operation are apt to be unduly copious in comparison with the meals eaten. This, as will be shown in the metabolism of these cases, is probably due to poor fat absorption in the early postoperative days.

REMOTE RESULTS OF GASTRO-ENTEROSTOMY. In studying the remote results (after six months) one must take into consideration (1) the mild or short cases, and (2) the severe or long cases. The former will settle down to their new normal level of health and permanent relief sooner than the latter. In regard to the late effects on (1) symptoms; (2) secretion; (3) motility; (4) longevity, it is possible to say that the relief of symptoms is permanent provided no complications exist and the ulcer heals. The secretions gradually settle down to their new normal, showing lower acid values than before or immediately following operation, but again often showing insignificant changes. It is among the late results that we do see occasional cases of achylia which before operation were hyperacid and showed hypersecretion, but in the main the secretory changes are much less than was formerly supposed. What the rule is that governs these changes in secretion, one case remaining hyperacid, another showing normal acidity, and still another achylia, when they were possibly all hyperacid before operation,

is entirely unknown, but just these irregular and apparently unaccountable results do occur. The late results in motility are the same as the early results when there is no atony, namely, early emptying time when both pylorus and gastro-enterostomy are patent, normal, or even delayed emptying time where the pylorus is occluded.

EFFECT ON LONGEVITY. As yet the modern operation of gastro-enterostomy has not been done for a long enough time to state definitely whether these cases live as long as normal persons do or not, but there are patients fifteen to twenty years postoperative who are in apparently perfect health.

Reasoning first by analogy it seems reasonable to expect this in cases that reach an uncomplicated end-result, although, of course, the operative risks diminish the life expectancy; but children operated upon by gastro-enterostomy for congenital pyloric stenosis grow, thrive, and reach normal young adult life as satisfactorily as their unoperated contemporaries.

The results of metabolism experimentation show a perfect utilization of the foodstuffs, as may be seen from the tables with the exception already mentioned under immediate operative results, in which we found copious stools, which are seen from the tables to be due in the early postoperative weeks to poor fat absorption.

ABSORPTION AFTER GASTRO–ENTEROSTOMY.

Subject and conditions. Case.	Time after operation, months.	Diet.	Fat absorbed, per cent.	Fat not absorbed per cent.	Nitrogen.	
					Absorbed, per cent.	Not absorbed, per cent.
1. Non-malignant[5]	5	Mixed	92.3	7.7	91.0	9.0
2. "	7	"	92.5	7.5	90.5	9.5
3. "	24	"	92.7	7.3	92.1	7.9
4. "	2	"	94.7	5.3	92.7	7.3

ABSORPTION AFTER GASTRO–ENTEROSTOMY.[6]

Condition.	Time after operation.	Sex and age.	Fat.		Absorb. gm.	In food. gm.	Nitrogen.	
			In food, gm.	In feces, gm.			In urine gm.	Absorb. gm.
Obst. pylorus	20 days	F. 40	69.0	8.60	87.5	7.2	7.5	97.1
Const. pylorus	36 "	F. 52	67.0	17.70	73.7			
No. obst. hematemesis	11 "	M. 53	118.0	15.90	88.6	14.7	11.5	93.9
Obst. dilatation	18 "	F. 43	122.5	5.25	95.7			
Duodenal ulcer	14 "	M. 41	201.5	7.00	93.5			
Stricture of pylorus	8 years	M. 68	126.5	8.07	91.2			

Also one case tested in the laboratories of the Presbyterian Hospital by Miss Granat, the then hospital chemist, showed two years

[5] Paterson: Hunterian Lectures, Royal College of Surgeons of England, 1906.
[6] Cameron: British Med. Jour., 1908, i, 144.

postoperative a perfectly normal nitrogeneous balance, fat absorption, and carbohydrate utilization.

When one now looks at the surgical statistics on the end-results of gastro-enterostomy it will be seen that in comparison with the medical results the percentage of cures is higher, apparently increasingly so as the cases are properly selected, operated upon by a competent surgeon, and *judiciously cared for and fed after the operation*. Very few people, however, would choose an operation if they could be cured by medical means, so that it is always well to remember that there are at least 20 per cent. of medically permanent cures—probably a much higher percentage.

SURGICAL END-RESULTS.—Joselin reports 82 cases of chronic ulcer treated surgically with these results: Cured, 47 per cent.; improved, 19 per cent.; unimproved and died, 34 per cent.

Peck[7] reports 74 cases of duodenal ulcer from the Roosevelt Hospital. Of these there were cured, 68 per cent.; improved, 7 per cent.; unimproved and died, 8 per cent. He was able to trace only 54 of the 74 cases, and of this number actually traced the cures were 84 per cent. Peck's results were a little less favorable in gastric ulcer.

Kuttner reported 1100 cases treated surgically, showing 65 per cent. cured.

Presbyterian Hospital records of 31 cases traced by the author showed: Cured, 64 per cent.; improved, 19 per cent.; unimproved and died, 19 per cent.

Martin and Carrol,[8] of Baltimore, report 45 per cent. unfavorable results in gastro-enterostomy and advise pylorectomy.

These surgical statistics show for this combined series of 1285 cases, 64 per cent. cured, as compared with the 20 to 40 per cent. cured medically, and also some of Kuttner's cases had gastro-enterostomy for other conditions than ulcer. (1) That the results are progressively more favorable as the operation has approached its present technical perfection, and (2) that there are still too many surgical failures. These failures may be traced for the most part to (1) poor operative risks; (2) a poorly selected and performed operation in the hands of inexperienced surgeons; (3) poor postoperative diet and care.

Mention has already been made of surgical failures from poor postoperative care and diet, but this point needs further mention, for it is of paramount importance if we are to get the best results obtainable in these cases of gastro-enterostomy.

Up to the present most surgeons have been extremely careless in the matter of postoperative diet, and one sees even now patients not yet two weeks postoperative, getting regular hospital fare, including, as it does, corned beef and cabbage. It is hard to explain

[7] Peck: Jour. Am. Med. Assn., August 21, 1914, p. 660.
[8] Ann. Surg., May 15, 1915, p. 557.

this lack of care on the part of some (but fortunately not all) surgeons, unless it is that the results in some cases, in spite of careless feeding, are so brilliant that the impression is gained that no particular care is necessary. But when one stops to consider the conditions present it seems little short of criminal to treat those cases as other than cases of ulcer still, until they have had a long enough time for thorough healing.

After operation the ulcer is still present and potent for evil, or it is possible to produce a jejunal ulcer on the jejunal wall opposite the new stoma by constant trauma of rough food plus a hyperacid gastric juice. All cases of gastro-enterostomy should be given, postoperative, a regular ulcer diet, giving the old ulcer the most favorable opportunity to heal and preventing food irritation elsewhere, notably at the site of the new opening, surrounded as it is by tender and vascular mucous membrane, or opposite the stoma, as already explained. The postoperative ulcer cure may be hurried rather more than under strictly medical conditions, but the fact remains that every opportunity for healing and cicatrization should be given, involving, as this does, weeks or months during all of which time the diet should be bland, soft, and free from all thermal, mechanical, or chemical irritants.

When this is systematically done we may hope in properly selected cases to get the percentage of surgical cures more nearly approaching the 100 per cent. mark, and too much stress cannot be laid on the importance of the food and drink factors in the attempt to attain perfect results.

STUDIES IN FRACTIONAL ESTIMATIONS OF STOMACH CONTENTS.[1]

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IN reviewing historically the advances in our knowledge of the chemism of the stomach in health and disease, one is forcibly

[1] These studies were carried on under the tenure of a George Blumenthal, Jr., Fellowship in Pathology.

impressed by the fact that since the introduction into clinical medicine of the stomach-tube by Kussmaul and its rapid adoption by the profession at large, little of great moment has been added to our fund of information regarding the pathological chemism of this organ under conditions of disease. Subsequently, and within a short period, hyperchlorhydria was differentiated from subacidities, achylia gastrica was recognized as an entity, the association of hyperacidity and hypersecretion established in their frequent relation to organic disease, and many other studies made.

The animal experimentation of the schools of Pawlow, Boldyreff, Heidenhein and others and the experimental roentgenographic work which followed have since then afforded a more accurate and scientific basis upon which to build our knowledge of the physiology of the stomach. Thus were the foundation stones for our understanding of the physiology of gastric secretion, gastric motility, the pyloric and cardiac reflexes laid down in vivisection. But the application of these facts to man remained theoretical rather than practical, due to natural limitations in the adoption of human clinical material to the conditions of animal research.

From time to time isolated studies on persons with fistulæ of the stomach or duodenum have added a few facts to those previously recorded. The classic observations of Beaumont are one of the best examples of studies carried out under the handicaps and conditions incident to human investigations. More recently, Hayem,[2] Bourget[3] and others attempted, by the method of introducing the stomach-tube at successive times in the course of digestion, to study the cycle of events taking place. This latter method was tedious, incomplete, and artificial.

As early as 1895 Schuele[4] published an article on the secretion and motility of the normal human stomach, as observed by means of a catheter which he left *in situ* throughout the cycle of digestion, thus simulating a gastric fistula. He was able to demonstrate the curve of acid secretion and actually ascertained many facts pertaining to secretion and motility, on diets of carbohydrate, fats, meat, etc. After a lapse of several years there occurred a renewal of interest in this method of studying the human digesting stomach, as was marked by the appearance of publications by Ehrmann,[5] Ehrenreich,[6] and Skaller.[7] Ehrenreich, in particular, made careful and accurate observations by means of a gastric catheter, withdrawing specimens by aspiration at frequent intervals. He was able to plot curves of acid and ferment secretion, to note the regurgitation

[2] Maladies de la Tube Digestif, 1905.
[3] Die Krankheiten des Magens, 1906, first edition, p. 17.
[4] Ztschr. f. klin. Med., 1895, xxviii, 461.
[5] Berl. klin. Wchnschr., 1911, xlviii, 2226.
[6] Ztschr. f. klin. Med., 1912, lxxv, 231.
[7] Berl. klin. Wchnschr., 1913, l, 2176; 1915, lii, 105.

of duodenal contents in normal and pathological cases, and to determine the effects on secretion and motility of the introduction of eggs, milk, etc.

Considering, however, that this method was the nearest approach to the conditions of animal research the subject did not receive the attention to which it was entitled. Further communications were absent until the recent revival of interest in the subject, as marked by the appearance of a series of articles by Rehfuss and his collaborators,[8] beginning in 1914. In these studies Rehfuss investigated by means of a catheter, to the distal end of which was attached a slotted metal capsule, the physiology of fasting and digesting stomach of normal persons; in small part he extended these studies to cover some diseased conditions. By frequent aspirations he was able to plot curves of acid and ferment secretion, ascertain the emptying time of the organ, secretion of mucus, etc. The observations of Rehfuss are of the greatest practical importance and bid fair to offer a method of studying gastric digestion far more complete and accurate than the single test-meal methods hitherto at our disposal.

A cursory review of the new facts thus brought to light is essential to the further understanding of the subject. Rehfuss determined that our idea of the fasting content of the normal human stomach was erroneous. While previously it had been held by Strauss,[9] Tuchendler,[10] Boas,[11] Bjorbjarg[12] and others that all amounts over 20 c.c. of fasting fluid were pathological, Rehfuss[13] demonstrated on apparently healthy medical students amounts varying from 30 to 120 c.c. Approximately 50 per cent. of these contained bile and trypsin regurgitated from the duodenum; most of them contained some free (20 to 40 per cent.), and some total acid (26 to 50 per cent.). This fact in itself was sufficient, in his opinion, to overthrow the contention of the above-mentioned authors that fasting contents of over 20 c.c., so-called "macroretention," was indicative of irritative hypersecretion in association with ulcer, cholelithiasis, and other organic conditions.

Rehfuss further established three types of secretory curves as normal, namely, the isosecretory, the hypersecretory or continued secretory, and the hyposecretory curve, depending on the rapidity of acid secretion, height of acidity attained, and maintenance of the

[8] AM. JOUR. MED. SC., 1914, cxlvii, 848. Rehfuss, Bergheim and Hawk: Jour. Am. Med. Assn., 1911, lxiii, 11, 909. Bergheim, Rehfuss, and Hawk: Jour. Biol. Chem., 1914, xix, 345. Rehfuss and Hawk: Jour. Am. Med. Assn., 1914, lxiii, 2088. Clark and Rehfuss: Jour. Am. Med. Assn., 1915, lxiv, 1737. Rehfuss: Jour. Am. Med. Assn., 1915, lxiv, 569. Fowler, Rehfuss, and Hawk: Jour. Am. Med. Assn., 1915, lxv, 1021.

[9] Deutsch. Arch. klin. Med., 1895, lvi, 87.

[10] Deutsch. med. Wchnschr., 1899, xxv, 390.

[11] Diag. u. Therap. der Magenkrankheiten, 1911, sixth edition.

[12] Arch. f. Verdauungskr., 1908, xiv, 251.   [13] Loc. cit.

acid crest to the end of the digestive period. He was unable to demonstrate a universal type of curve for all persons. A few cases of gastric ulcer, gastritides, and other conditions were observed, but too few from which to draw conclusions. Achylia gastrica was studied thoroughly, and those cases of spurious achylia (those in which there is a rise of acid toward the latter half of digestion) differentiated from those in which the achylia is true and constant throughout.

In the following studies we have attempted to apply the method of fractional estimation of gastric contents to persons suffering from abdominal symptoms and to ascertain to what extent and in what degree pathological processes and abnormal stimuli alter the cycle of digestion, the emptying time of the stomach, the factor of duodenal regurgitation, etc.

The studies are based upon over 200 curves taken from patients in the medical wards and dispensary of the Mt. Sinai Hospital, representing all phases and varieties of abdominal disease. In a large percentage of the cases the clinical diagnosis was confirmed by operation. Throughout, the attempt has been made conscientiously to consider only such cases in which the symptoms have been clear-cut and definitely indicative of pathological conditions.

EXAMINATION OF THE FASTING CONTENTS. Our technic has been to require the patient to swallow the Rehfuss tube[14] at 8 A.M., all other food or drink having been proscribed since the evening meal of the previous day. When the question of pyloric obstruction arose, the patient ate on the previous night at 10 o'clock thirty raisins with the skins and seeds. The swallowing of the tube is actually an easy matter; we having never encountered a single patient who has declined or been unable to accomplish it. Retching is avoided to the greatest possible degree to prevent the tendency to regurgitate duodenal contents into the fasting organ. The stomach was aspirated in several positions until no futher material was obtainable.

The fasting contents were usually clear, watery, or slightly turbid in appearance. In about one-quarter of the cases bile was present in amounts varying from a slight tinge to a heavy golden-yellow color. Except in cases in which gastro-enterostomy had been performed (in these bile was constantly present and in large amounts) there appears to be no definite clinical significance to the appearance of bile in the fasting contents. When present it denotes a patent pylorus. It may be persistently absent in organic pyloric stenosis but is usually present in functional pylorospasm. There is no question that in the process of swallowing the tube some retching,

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[14] The Einhorn duodenal tube (Medical Record, 1910, lxxvii, 98), is equally serviceable and answers all purposes; it was frequently used. A gastric tube devised by M. Gross (New York Med. Jour., 1893, lviii, 600), was probably the first tube of its kind to be suggested for such a purpose.

if only slight, invariably occurs, and as the acts of vomiting and retching are associated with a relaxation of the pylorus it is easily comprehensible that this will explain, in a large number of instances, the presence of bile in the fasting contents.

The amount withdrawn from the fasting stomach varies from nothing to 140 c.c. It rarely happens that nothing is withdrawn. This series includes practically no absolutely normal cases, but the experience of Rehfuss and his collaborators is highly interesting in that he was able to demonstrate in normal individuals amounts varying from 20 to 120 c.c. In our series the amounts recovered were as follows: gastric neuroses, 2 to 60 c.c., averaging 31 c.c.; gastric or duodenal ulcer, 20 to 140 c.c., averaging 54 c.c.; cases of chronic appendicitis, 30 c.c.; marked subacidity or achylia cases were either empty or showed at a maximum 10 to 25 c.c.; functional hypersecretion 50 to 70 c.c.

We were unable at any time to duplicate the large amounts found by Rehfuss and his co-workers in normal males, or of Fowler and Zentmire[15] in normal or approximately normal females. In our series the larger amounts seen with ulcer are suggestive of the hypersecretion which so frequently accompanies this condition and supports the contentions of Rubow,[16] Bamberger[17] and others on this point. Bamberger, for instance, designates as "macroretention" amounts over 21 c.c. and found this in 55 per cent. of real ulcer cases, and in 58 per cent. of hypersecretion cases, in which latter group the possibility of ulcer was a likely one. It should be noted, however, that his stomach contents were removed with the older and more usual type of stomach-tube.

The acidity of the fasting residue varies considerably, but follows in general the acid titration of the digesting meal. The acid titer is never above that of the test breakfast; usually it is lower than its maximum; in cases of hyperacidity it is materially lower. But in those cases which approximate the normal curve, the total acid of the fasting content is usually near the same figure as at the end of the fractional test meal. This should be designated as the "minimal acidity" of the stomach. In cases with normal or slightly hyper-acid curve, the fasting titration shows free acid of 32 to 52 per cent.; total acid of 44 to 68 per cent. In subacidity cases free acid is absent, total acidity diminished to 20 per cent.

Mucus in small amounts was present in all cases, the origin in part being salivary mucus, in part the secretion of the pyloric antrum. It is the deglutitory effort which increases the amount of the fasting contents found by this method, and makes the presence of salivary mucus, in small amounts fairly constant. On the other hand, cases of chronic gastritis, marked subacidity, and carcinoma

15 Jour. Am. Med. Assn., 1917, lxviii, 167.
16 Arch. f. Verdauungskr., 1906, xii, 1.   17 Ibid., 1911, xvii, 241.

exhibit usually a marked increase in mucus which sediments out in a heavy layer on standing.

Food particles recovered by this method have the same significance as when found by any other method, namely, are highly suggestive of pyloric obstruction. Raisins given the previous night appear as shreds of raisin skins in the aspirated contents. When food residue occurs a higher acidity titration is the rule, as the organ, never being free of the food stimulus, continues to secrete acid of digestive concentration; that is, its "minimal acidity" is raised. Blood has been noted only in cases of carcinoma. Sarcinæ and yeasts are occasionally found and have the usual significance.

THE TEST BREAKFAST. A heavy oatmeal gruel was utilized as the test meal. The gruel was made by adding two heaping table-spoonfuls of oatmeal to a quart of water and boiling it down, over a small flame, until it was reduced to a pint in volume. The gruel was then filtered through gauze to remove the solid particles; a pinch of salt was added to make it more appetizing, except when chloride studies were being made. After he had successfully swallowed the tube and the fasting contents had been aspirated, the warm gruel was given to the patient to drink. If a large fluid residue remained in the fasting stomach from the previous day, gastric lavage was first practised, because the test was always performed on an empty stomach. Every fifteen minutes thereafter 10 to 15 c.c. of the contents of the stomach were aspirated for examination; the aspirations were continued until the stomach became empty.

THE ACIDITY CURVE. Every specimen was titrated for free and total acid and the resulting amount expressed in cubic centimeters of decinormal sodium hydrate per 100 c.c. of stomach contents. A curve, based on the results, was then plotted. The appearance of bile in the aspirated fractions was carefully noted. The emptying time of the organ was estimated by the disappearance of the starch reaction as determined by the addition of tincture of iodin in excess to each tube. The presence of mucus was carefully noted; rennin and pepsin were tested for in cases of anacidity, and the Wolff-Junghans test performed in cases suspected of carcinoma.

As the clinical material at our disposal included practically no normal cases we do not feel able to demonstrate curves of entirely normal persons. However, in the course of collecting so large a series one sees many curves which are practically normal, as judged by the standards set by Rehfuss and his co-workers in their investi-gations of the stomach of students free from disease. Many cases were noted which corresponded to the three types of normal secretory activity, namely, the isosecretory, hyposecretory, and the hyper-secretory or continued secretory classes. The publications of these investigators clearly demonstrated these curves on normal indi-viduals. In a group of cases numbering over 50 instances, in which are included all cases free from organic disease, we noted many

illustrations of these normal curves. The pure gastric neuroses and the so-called normal cases (hernia, etc.), fall easily into this group. Free acid appeared soon after the beginning of the test; maximum total acidity (60 to 70 per cent.), was reached at about one hour; thereafter there was a slow decline approaching the base line, though never quite reaching it. The stomach emptied itself usually in two or two and a half hours. The course varied but slightly in the hypersecretory cases, the total acidity reaching slightly higher levels to 80 per cent. and over. These latter cases empty themselves in the same time, though the fall of the acidity was slower and did not approach the base line until later, if at all. The hyposecretory type
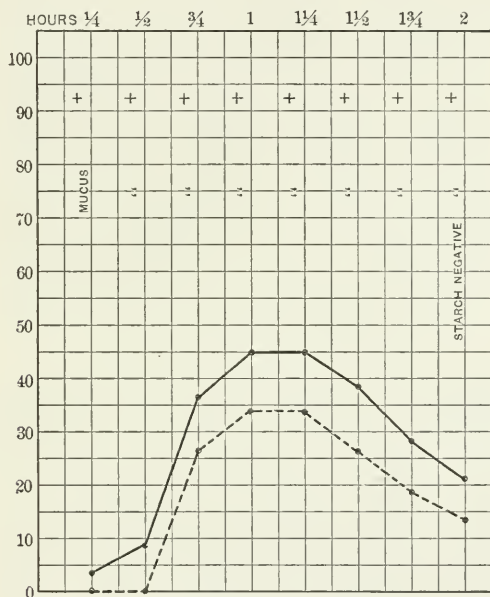
Fig. 1.—Isosecretory type.

was essentially the same as the isosecretory, the acid not rising above 50 per cent., emptying time being usually two hours (Figs. 1, 2, and 3).

A regurgitation of bile normally took place as the height of digestion was passed, that is, about one and a quarter or one and a half hours after the meal. This regurgitation frequently increased as the digestion approached conclusion and should be regarded as a phenomenon consistent with a healthy functionating stomach. No relationship could be traced between the degree of biliary regurgitation and the fall of acidity toward the end of digestion, bile being often abundantly present with a sustained acidity, while conversely the fall of acid may have been sharp and yet no reflux

of duodenal contents have taken place. Nor has the presence of mucus been in any way consistently proportionate to the fluctuations of acidity or to the fall of acidity at the end of digestion.
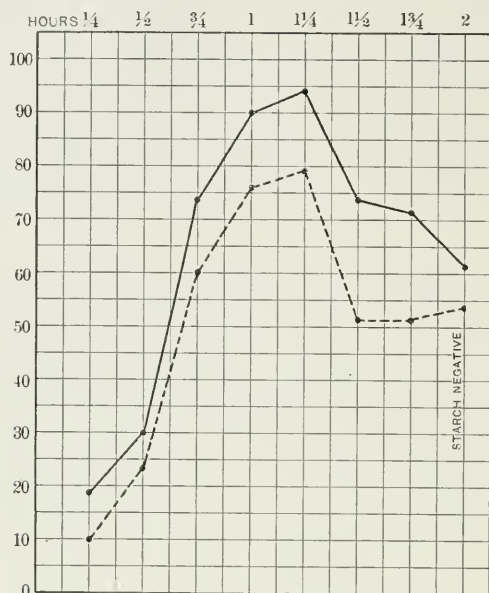
FIG. 2.—Hypersecretory type.
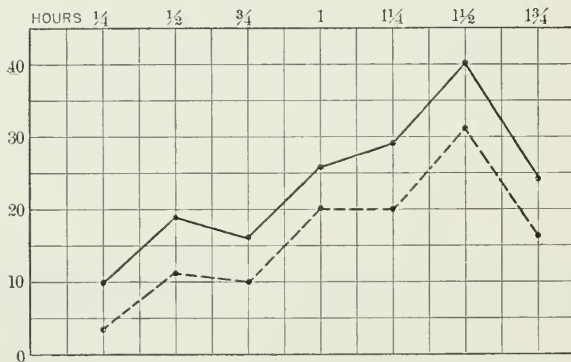
FIG. 3.—Hyposecretory type.

While it was true, as a rule, that the height of secretory activity occurred at one hour after the ingestion of the gruel, exceptions were not at all infrequent; one of the advantages of this method consisted in discovering such instances of late secretory activity, and in a few cases of premature activity. Thus Fig. 4 illustrates a case with total acidity of 24 per cent. at the end of one hour, while half an hour later the acidity had reached 92 per cent.

An illustration of earlier secretory activity is afforded in Fig. 5, in which the height of acidity (54 per cent.) was reached at three-quarter hours, while at one hour it was only 36 per cent. However,

Fig. 4.—Late hyperacidity.

Fig. 5.—Early rise in acidity.

these cases were not by any means frequent, and in those cases free from organic or secretory derangements the height of digestion took place at one hour.
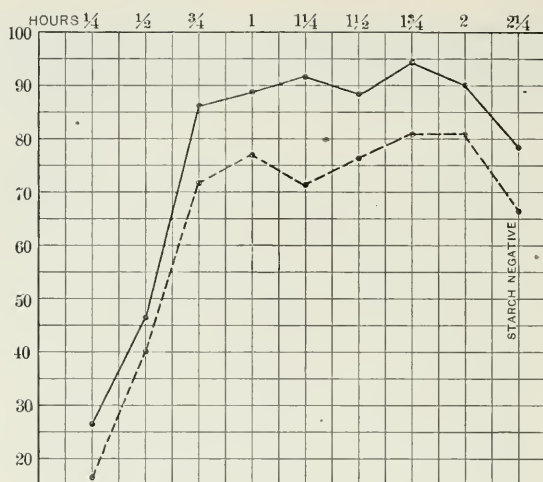
Fig. 6.—Simple hyperacidity.
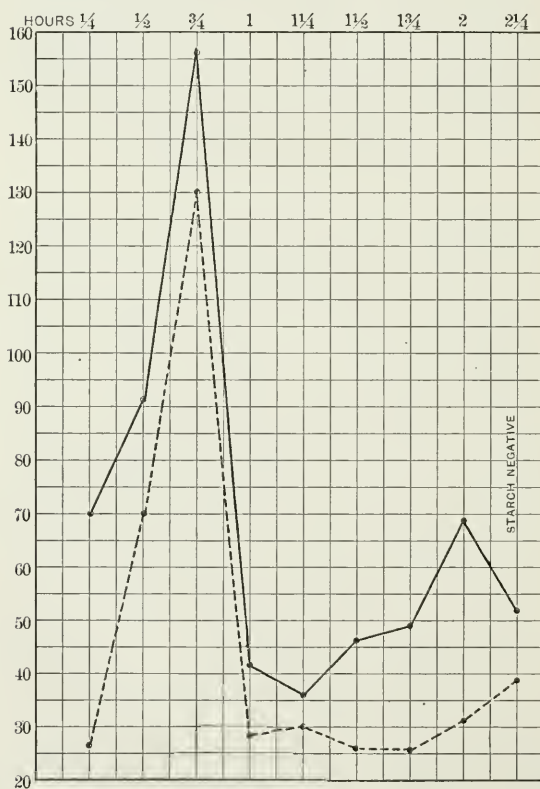
Fig. 7.—Neurosis.

FUNCTIONAL SECRETORY DISTURBANCES; HYPERCHLORHYDRIA. These cases are those in which the total acidity rose rapidly and higher than in the normal cases, though the emptying took place in the usual time. In general the figures obtained by this method, using the oatmeal gruel as a test substance, were lower by comparison than those after the Ewald test breakfast of a roll and tea extracted after one hour. The hyperacidity ranged between 80 and 110 per cent. and often reached 130 and 140 per cent., or
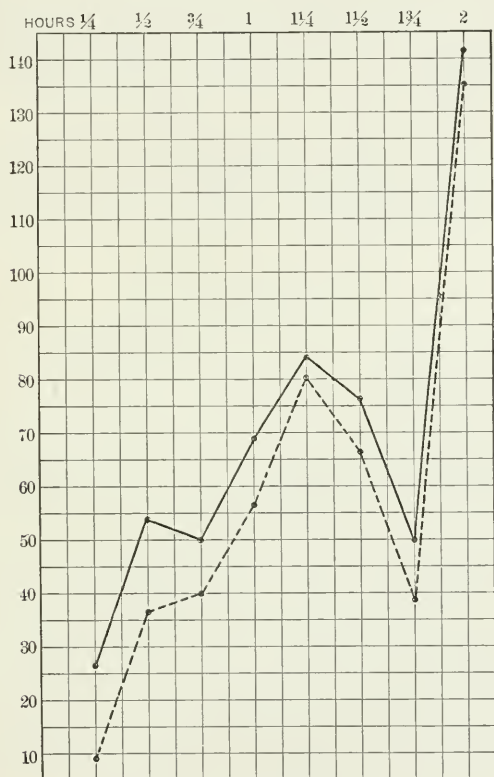
FIG. 8.—Neurosis hyperacidity.

exceptionally higher. Fig. 6 illustrates a case of simple hyperacidity. Fig. 7 is an illustration of larval hyperacidity in which the total acidity at three-quarters of an hour was 148 per cent., while fifteen minutes later it was 42 per cent. In Fig. 8 one sees an example of late hyperacidity in which at one and three-quarter hours the total acidity was 40 per cent., while a quarter hour later it was 142 per cent.

CASES OF HYPERSECRETION. This type of case is a most interesting one to study, for the secretion of gastric juice may continue for

hours after the normal period of digestion. A reference to Fig. 9 will show a case of hypersecretion in which, for several hours after the stomach was free of all starch, a clear watery secretion of pure gastric juice continued to be secreted. Or, Fig. 10, a case of migraine with hypersecretion in which a watery juice continued for six hours after the ingestion of the meal. A delay in motility was apparent throughout, as even at the end of the six hours starch was present. To determine the nature of the hypersecretion, the stomach
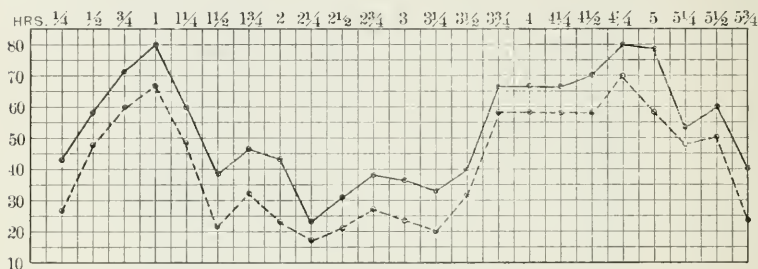
FIG. 9.—Continued hypersecretion.

was completely emptied at the end of the six hours, 165 c.c. being obtained. The secretion of gastric juice immediately ceased (alimentary hypersecretion). That this case was one of pure functional disturbance was proved by the fact that at exploratory laparotomy no organic disease was present and the pylorus admitted two fingers. In another case, probably associated with ulcer, the secretion continued in spite of emptying the stomach of all residue
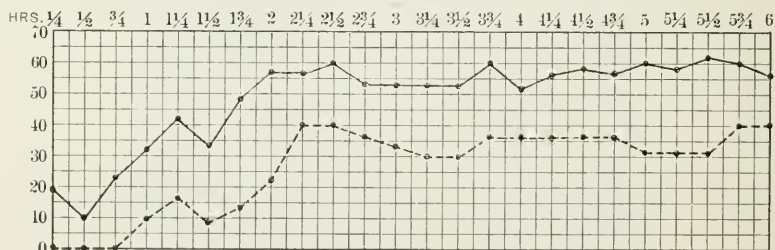
FIG. 10.—Alimentary hypersecretion.

(continuous hypersecretion). The hypersecretion continued without cessation, the experiment being interrupted only by the fatigue of the patient.

ANACIDITY AND ACHYLIA GASTRICA. In cases of anacidity there was a lack of free HCl throughout, though the total acid may have risen to 20 to 30 per cent. at some time of the digestion. Ferment strengths were maintained, fasting contents were usually absent or of minimal quantity, and the stomach emptied itself within two

hours. In the achylia cases free acid was consistently absent
throughout; total acid fluctuated between the extremely narrow
limits of 8 to 10 or at most 14 per cent. The emptying time was
shortened to one and a half or one and three-quarter hours; ferments
were absent (Fig. 11). A rise of acidity was uncommon at any time
of digestion, although it occasionally occurred. A distinct classi-
fication of psychical and chemical achylias we have been thus far
unable to confirm. Since achylia gastrica should be regarded merely
as an advanced stage of anacidity, those cases with late rise of acidity
belong properly to the class of anacidity, rather than create a new
classification of "spurious achylia" (Rehfuss). Some of the most
advanced examples of achylia occurred in cases of pernicious anemia;
ferments as well as mineral acid were lacking in these instances.
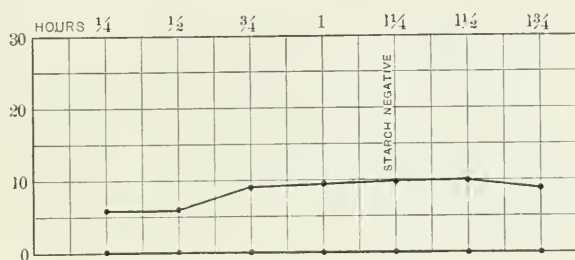
Fig. 11.—Achylia gastrica.

ORGANIC DISEASES; GASTRIC OR DUODENAL ULCER. While it
cannot be said there is a curve absolutely characteristic for ulcer,
yet it may conservatively be stated that ulcer cases are associated
with a curve of acidity that rises rapidly and is sustained if not
throughout the cycle of digestion at least to within a short time
(fifteen minutes) of its end. It is not the height of the curve of
acidity that makes one suspect ulcer, for that could as well be the
case in functional hyperacidity; it is the steady, rapid, prolonged
rise and sustained plateau seen so consistently in ulcer cases (Fig. 12).
The fall of acidity, if it takes place at all, occurs just before the
final emptying of the stomach. A delayed motility was frequently
a factor and indicated pyloric involvement, either functional or
organic. The regurgitation of bile was most commonly absent or,
when present, took place only at the very last phase of the digestion.
The presence of mucus was not associated with ulcer, though
occasionally it was seen in large amounts in the fasting contents and
at the termination of the period of observation. In spite of what
might have been expected, blood was absent throughout; a trace
of blood was seen only once in a case of gastric ulcer and then in
only one of the specimens withdrawn. Very little trauma was
associated with this method of test meal and the presence of blood
had therefore all the more significance.

The highest acidity seen was 116 per cent., occurring once one and a half hours and in another instance two and a half hours after the onset of digestion. In all of these curves the highest acidity
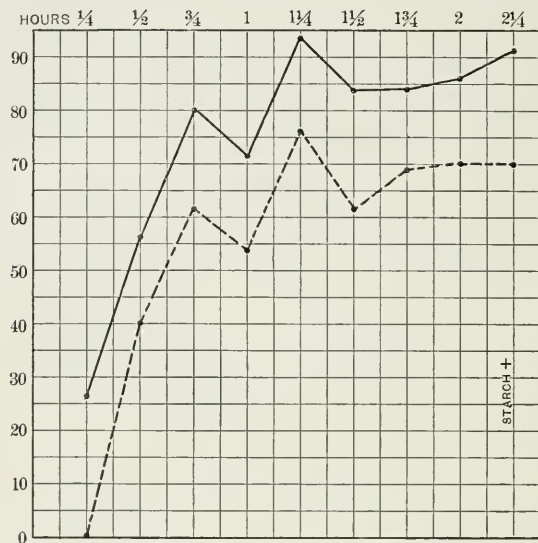
FIG. 12.—Ulcer of duodenum.
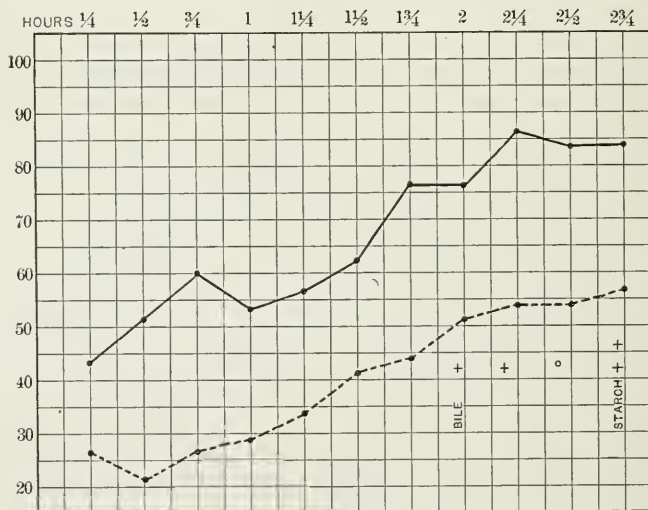
FIG. 13.—Pyloric stenosis.

took place not one hour after eating but one and three-quarter to two and a half or three hours after giving the test breakfast. This was a constant phenomenon. No case of subacidity had been noted

in this series of ulcer curves. A mild hypersecretion was occasionally noted; after the starch had entirely left the stomach a strong acid secretion may continue for a half to two hours longer. This postdigestive secretion was clear, watery, contained little or no mucus and no bile. Chemical analysis of this fluid shows it to correspond closely to the analyses of pure gastric juice as found in the standard text-books. The hypersecretion was evidenced on the charts by the approach of the curves of free and total acid secretion. This was easily comprehensible when one considers that with the emptying of the stomach the protein in the test meal leaves the organ, diminishing the amount of the combined acid. The pure acid juice thereafter secreted contains only very small amounts of proteins or acid phosphates, as indicated by the narrow difference between the free and total acidities at this point.

Cases with pyloric stenosis show moderately high acidity at the outset (30 to 50 per cent.), and in addition exhibit a gradually ascending curve which was highest at its end and showed no tendency to drop. Motility was, of course, delayed (Fig. 13).

CHOLELITHIASIS; CHRONIC APPENDICITIS. To date we have found no possible means to differentiate these curves from those of ulcer. Hypersecretion was not observed, motility not delayed.

POST-GASTRO-ENTEROSTOMY CASES. These cases show normal or subacid curves; occasionally, in cases with recurrent symptoms of long duration, anacidity. The curves were characterized by a drop in acidity which took place at the end of the first hour; this drop was associated with a regurgitation of intestinal contents and was followed by a secondary rise in acid. The regurgitation of intestinal contents once begun, continued to the end of digestion. Cases after operation, with recurrent symptoms due either to functional disturbance of the motor and secretory mechanism or to organic stenosis at the stoma, exhibited a more prolonged secondary rise with a delayed motility lasting up to two hours or more, usually three hours. In cases with unduly large stoma a free regurgitation of intestinal contents into the stoma may occur not only throughout digestion but in the fasting state as well. The test meal leaves the organ early, yet the stomach is never empty. The delay in the emptying of the stomach, so often seen after the operation of gastro-enterostomy, was frequently a manifestation of the disturbed motor mechanism of the organ, as described more fully in a recent paper by Wilensky and Crohn.[18]

CARCINOMA VENTRICULI. These curves are those of marked subacidity, occasionally of anacidity. The almost flat curve of achylia was rarely seen (Fig. 14). The gastric ferments, rennin and pepsin, were retained in all the cases. Blood, which was prac-

18 AM. JOUR. MED. SC., 1917, cliii, 808.

tically never seen in other conditions, was very common, occurring toward the end of digestion, usually in several of the specimens as well as in the fasting contents. When blood was present the individual curves of free and total acid became divergent, due to the large amount of combined acid formed from the blood protein. Mucus was frequently abundant. We were unable to draw diagnostic conclusions from estimations of soluble albumin performed by the Wolff-Junghans method.
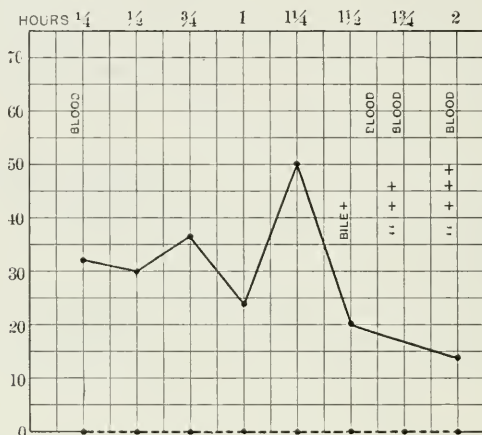
FIG. 14.—Carcinoma.

MISCELLANEOUS. Chronic parenchymatous nephritis, the convalescent stage of acute intercurrent infections, syphilis of the stomach, give the curve of subacidity without novel characteristics.

The DIAGNOSTIC SIGNIFICANCE OF THE CURVES. UTILIZATION OF THE METHOD. One who expects to find in the curves of the fractional estimation of stomach contents new and infallible diagnostic criteria will be disappointed. One who hopes to label each type of curve as representative of a particular disease will raise false hopes. On the other hand, many of the curves are highly suggestive of certain diseases. There is a type of curve quite constant for ulcer; cases of hypersecretion; anacidity, achylia, and postgastroenterostomy cases show clear-cut types, individually representative of these conditions and easily recognized. For the demonstration of digestive hypersecretion the method is unequalled. But the importance and greatest value of the method lies in the fact that it offers knowledge regarding the physiology of the entire cycle of digestion from the beginning fasting state through to the very end of the digestive period. We are in a position to gain information regarding the following points:

1. Fasting contents: amount, presence of food residue, presence of regurgitated bile, mucus, or blood.

2. Type of secretory activity as regards free and total acid, namely, the acid curve.

3. Duration of secretory activity, whether ceasing with the exit of the food or maintained as a hypersecretion thereafter.

4. Time of emptying of the stomach, that is, its motility.

5. Presence of mucus and time of occurrence.

6. Presence of bile, as indicative of pyloric relaxation and duodenal regurgitation.

If we are accustomed to draw diagnostic conclusions from the usual test meal at the end of one hour, we can surely form a better opinion with the added information which this test affords.

While the method may not give a finished diagnosis it gives numerous facts which when properly interpreted and pieced together we recognize as indicative of functional disturbance of the stomach associated with a particular disease. It combines in itself the best features of several of the well-known test meals, namely, the Ewald, the Riegel (motility test dinner), and the Boas oatmeal test for presence of lactic acid. It makes superfluous the complicated mathematical formulæ of the Mathieu-Rémond method for estimating motility.

A disadvantage of the method is the time required for its completion. In institutional work this is less of a factor, as the nurse can easily aspirate every fifteen minutes until the stomach is empty.

Recently, Best,[19] in a thorough review of the subject, strongly emphasizes the advantages which this method has over the single test meal, recommending it for further serious consideration at the hands of the profession. Fishbaugh[20] warmly recommends the method and calls attention to the insufficient, often misleading information furnished by the one hour test, as controlled by the fractional method. Andresen and d'Albora,[21] in an accurate estimation of many curves, found some very typical curves, as of duodenal ulcer and achylia.

For the scientific study of the chemism of the stomach in its departure from health to disease this test must take its place as one of the most valuable adjuncts to our present methods. Its field of usefulness for the study of the effects of medication, dietary therapy, psychical influences, operative procedures, etc., is unlimited.

We take pleasure in thanking Drs. Brill, A. Meyer, Manges, and Libman, attending physicians to the medical services of the hospital, and Dr. Aronson, chief of the department of gastroenterology of the dispensary of the Mt. Sinai Hospital, for their kind permission allowing us to study the clinical material at their disposition.

[19] Jour. Am. Med. Assn., 1916, lxvii, 1083.   [20] Ibid., p. 1275.
[21] Long Island Med. Jour., 1916, x, 133.

THE ACTION OF OPIUM AND SOME OF ITS ALKALOIDS ON THE DIGESTIVE TRACT.

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Opium and morphin are used by most physicians promiscuously and interchangeably in the many conditions in which an opiate is indicated. Perhaps the only difference between the two recognized by the average practitioner is that morphin can be administered by hypodermic injection while opium must be given by mouth. With the appearance on the market of soluble preparations of total opium alkaloids such as pantopon or pantopium, even "opium" can be given now by injection, and this difference therefore also disappears. A great many men regard morphin therefore as simply a more concentrated form of opium.

Recent investigations, however, on the pharmacological action of various opium alkaloids have revealed that the so-called "minor" alkaloids of opium play a very important pharmacological and therapeutic role and render the properties of opium as such or of combinations of its various alkaloids radically different from those of its principal alkaloid, morphin, when given alone.

Thus the author[1] has shown that the effect of opium and of various combinations of its alkaloids on the respiration is in important respects very different from that of morphin. In another investigation the author[2] has shown that the analgesic properties of morphin and opium are quite different, and in a still further investigation the author[3] has recently called attention to the difference between opium and morphin in their effect on the ureter in kidney colic.

The action of opiates on the alimentary canal is one of the cardinal therapeutic indications for their administration. This action has been carefully studied by a number of observers, notably by Nothnagel, Magnus, Pal and others. The most fundamental facts on the subject, however, are so little known to the average physician and are so poorly described in most text-books that it was thought desirable to review them briefly in this place, and in addition to report some original investigations recently conducted by the author.

CHEMISTRY. In order to understand the pharmacology of opium it is essential to know something of its constitution. This is very complex. Up to the present time opium had yielded some twenty-two different alkaloids, besides protein bodies, sugar, gum, resin,

[1] Macht, Herman and Levy: Jour. Pharmacol. and Exper. Therap., 1915, vii, 339.
[2] Macht: Ibid., 1916, viii, 1.   [3] Macht: Ibid., 1917, ix, 197.

inorganic salts, and organic acids. Of the alkaloids some are present in very minute quantities, and, so far as we know at present, play an unimportant role. Half a dozen of the alkaloids, however, occur in larger quantities, and are now known to be of great pharmacological importance.

The six principal alkaloids of opium, in point of quantity and importance, and their relative percentages of opium, are as follows:[4]

Morphin	. . . .	10.0	per cent.
Narcotin	. . . .	6.0	"
Papaverin	. . . .	0.1	"
Codein	. . . .	0.3	"
Narcein	. . . .	0.02	"
Thebain	. . . .	0.01	"

These six alkaloids in respect to their chemical structure are divided into two distinct classes: the pyridinphenanthrene and the benzylisoquinolin groups.[5] Morphin, codein (methylmorphin) and thebain (dimethylmorphin) are members of the pyridinphenanthrene group. Papaverin, narcotin, and narcein are members of the benzylisoquinolin group. The importance of this classification will be seen later. From the composition of crude opium it is evident that the galenical or ordinary pharmaceutical preparations of opium are not adapted to hypodermic administration. For subcutaneous use, however, combinations of opium alkaloids minus the inert and insoluble constituents have been introduced. The best known of these are pantopon, prepared by the Swiss pharmacologist, Sahli,[6] which is a mixture of the hydrochlorides of the total opium alkaloids containing 50 per cent. of anhydrous morphin (about five times as much as in crude opium) and narcophin, which is a mixture of morphin and narcotin meconates in the proportion of one to two.[7]

ACTION ON THE VOMITING CENTER. Nausea and vomiting are among the commonest sequelæ which the physician encounters after administration of opium, and especially of morphin. These untoward symptoms, which may occur even after very small doses of morphin, although not dangerous in themselves, are disagreeable enough to be largely responsible for the employment of other opiates in its stead either in the form of the individual alkaloids, such as codein or dionin, or of various combinations. The vomiting produced by morphin has been conclusively shown to be of central origin, that is, to be produced by stimulation of the vomiting center in the medulla. This is proved by the fact that it occurs soon after injection of morphin subcutaneously or intramuscularly, and is still further confirmed by the interesting experiments of Hatcher and

[4] Simon: Dissertation, Berne, 1903.
[5] Winterstein and Trier: Die Alkoloide, Berlin, 1910.
[6] Therap. Monatsh., 1909, xxii, 1.
[7] Macht: AM. JOUR. MED. SC., 1916, clii, 16.

Eggleston,[8] who, having eviscerated dogs, were still able to produce retching movements of the abdominal muscles on injecting the drug. Considerable individual variations occur in men in respect to the nauseating and emetic action of morphin. In dogs morphin is a specific emetic, almost as much so as dehydromorphin or apomorphin is a specific emetic for men.

The author has for some time past been conducting experiments on dogs and making observations on patients for the purpose of determining the comparative effects of various opium alkaloids individually and in combination with each other on the vomiting center.[9]   It was found on injecting dogs with the six principal opium alkaloids—morphin, codein, narcotin, papaverin, narcein, and thebain—that in respect to their emetic effect they fall into two groups: on the one hand morphin, which produces nausea and vomiting very easily, and even after small doses of the drug, and, on the other hand, all the other alkaloids which induce vomiting very rarely, even after very large doses.   Thus, 50 to 100 mg. of codein per kilo weight of dog were not followed by emesis, whereas doses of morphin 0.4 mg. per kilo usually produced vomiting.   The minimal dose of morphin to prove effectual showed considerable individual variations; in some cases as little as 0.15 mg. per kilo being sufficient to produce vomiting, in other cases larger doses being required.   The average usual dose was found to be between 0.3 and 0.4 mg. per kilo weight of dog.   Such doses of morphin not only produce vomiting, but also tended to paralyze the vomiting apparatus after the emesis, so that a subsequent injection of apomorphin did not prove effectual.

Parallel to the morphin experiments a series of observations on the same animals but on different days were made with combinations of various opium alkaloids.   Here a remarkable phenomenon was noted.   It was found that a combination of morphin with narcotin or of morphin with papaverin (narcotin and papaverin being members of the benzylisoquinolin group) do not produce vomiting as often as the same dose of morphin does when given alone.   Furthermore, it was noted that such a combination tended less to put the vomiting mechanism out of commission, so that a subsequent injection of apomorphin was usually effectual and produced vomiting, whereas the same dose of morphin when given alone paralyzed the vomiting center, rendering response to apomorphin negative.   Thus the average dose of morphin that could be administered in combination with narcotin without producing vomiting was 0.5 mg.

Even more striking was the effect of morphin when administered in the form of the total opium alkaloids or pantopium.   In this combination doses of morphin much larger than the usual emetic

[8] Jour. Pharmacol. and Exper. Therap., 1915, vii, 225.

[9] Macht: Tr. Assn. Am. Phys., 1916, p. 440.

dose of that alkaloid could be administered without the production of vomiting and without paralyzing the vomiting center, as indicated by its response to he subsequent injection of apomorphin.

· Following the above experiments on dogs a series of observations were made on the author himself and some co-workers, and later on ambulant patients, who required an opiate as a sedative, on the relative nauseating or emetic effect of morphin, morphin-narcotin (narcophin), and total opium alkaloids (pantopon). Here again it was found that morphin was much more nauseating when administered alone than when given in combination with other opium alkaloids. As little as 4 or 5 mg. of morphin by itself were in some cases sufficient to produce nausea. On the other hand, 20 mg. of Sahli's combination (= 10 mg. of morphin) seldom produced nausea or vomiting. An exhaustive examination of the literature on the subject was found to confirm the author's experience.

The practical deductions from the above investigation are in the first place that morphin alone is more nauseating than when given in combination with other opium alkaloids, and in the second place that even minute doses of morphin, doses which are insufficient for the relief of pain, may nevertheless produce nausea. It is therefore not logical to decrease the dose of morphin for the purpose of eliminating its nauseating effect. It is interesting to note that the above experimental results agree well with the empirical observations of some older clinicians. Thus, for instance, Fronmüller,[10] in his interesting work on *Opium and Its Alkaloids*, states that opium, on the whole, is less nauseating than morphin.

ACTION ON THE STOMACH. In addition to the nauseating and, what is always an accompaniment of emesis, the salivating action of morphin, several other effects produced by that alkaloid and by opium on the stomach must be mentioned.

The absorption from the stomach, insofar as it takes place, does not seem to be interfered with by these drugs.

The secretions of the stomach are, however, markedly decreased.

A very interesting point to be noted is the excretion of morphin by the stomach wall. The drug, after having been absorbed from the intestines, is reëxcreted by the gastric mucosa. Indeed, even after hypodermic administration of morphin a considerable percentage of it is excreted into the stomach and can be recovered by washing it out. This is of practical importance and suggests lavage as a rational procedure in all cases of opium or morphin poisoning.

Perhaps the most striking effect of morphin on the stomach is the pylorospasm following its administration. Morphin causes a powerful tonic contraction of the pylorus which lasts for many hours, as may be demonstrated by roentgen-ray studies. This pylorospasm is regarded by Magnus[11] as one of the principal factors

[10] Klinische Studien über die narcotischen Arzneimittel, Erlangen, 1869.
[11] Pflüger's Arch., 1908, cxxii.

tending to produce constipation after morphin. Opium, or the total opium alkaloids, does not produce such a powerful spasm of the pylorus.

The decrease in secretion and the pylorospasm are in large measure responsible for the indigestion following the administration of morphin.

Finally, we may mention the remarkable anorexia or loss of appetite produced by morphin and opium. It is well known that morphin fiends and opium-eaters can go for long periods of time without food, owing to the impairment of digestion and loss of appetite consequent to the taking of the drugs.
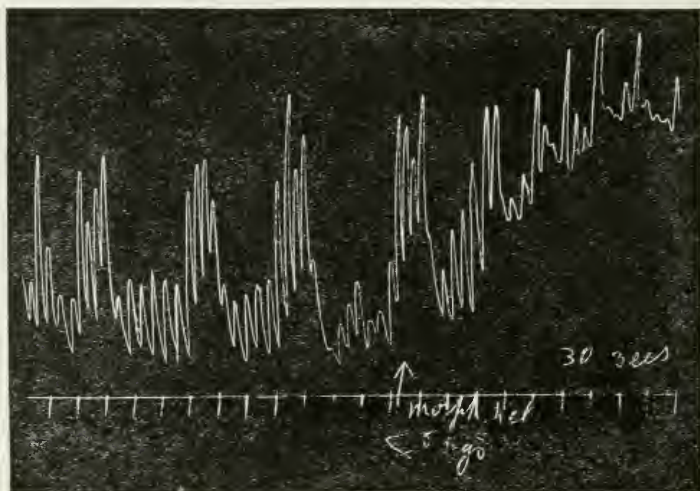
FIG. 1.—Intestine of cat. Segment 2 cm. long. Contraction = up-stroke. Showing stimulating effect of morphin, 5 mgm., in 30 c.c. Locke's solution.

ACTION ON THE INTESTINES. In respect to their action on the intestine important differences are to be noted between morphin and opium. In order to understand these it is necessary to examine somewhat in detail the action of morphin on the one hand and of the so-called "minor" opium alkaloids on the other.

When the action of morphin is studied on a segment or a loop of isolated intestine it is found that it powerfully stimulates the peristaltic movements and decreases the tonus of the organ, through an action on Auerbach and Meissner plexuses situated in its walls. A similar effect is produced by the other alkaloids of opium which belong to the pyridinphenanthrene group, namely, codein and thebain (Figs. 1 and 2).

The sedative or constipating action of morphin, when it occurs, is due to a number of other effects produced by it, and which counter-

act the above-described stimulating action. Of these the most important are as follows: (1) A spastic contracture of the pylorus, already described above. This hinders the passage of food from the stomach into the gut and in this way deprives the latter of one of its natural stimuli. Magnus, in a very elaborate study, regards this as one of the chief causes of constipation after morphin. (2) There is a similar tonic contraction of the ileocecal sphincter which tends further to hinder the passage of fecal matter. (3) In the third place there is a diminution in the pancreatic and enteric secretions[12]
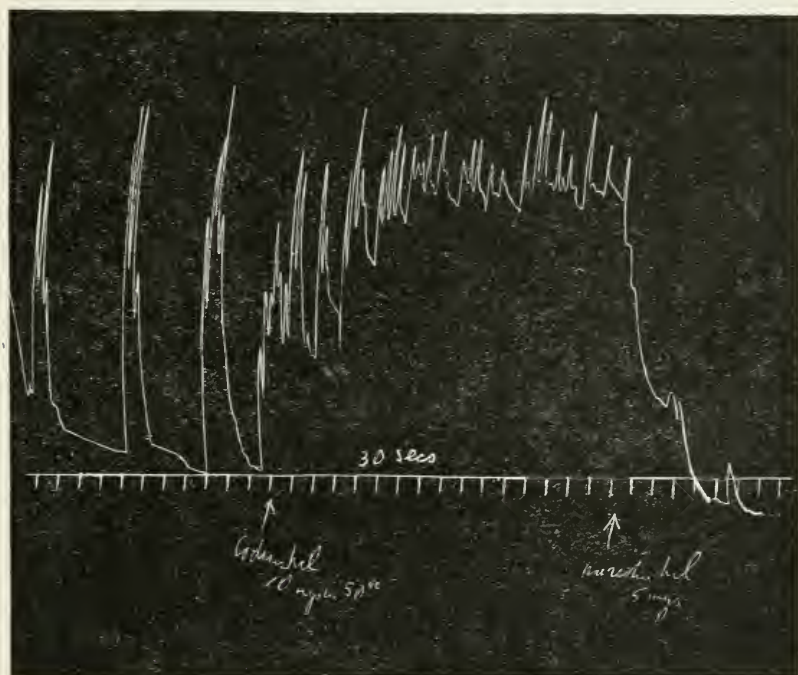
Fig. 2.—Intestine of cat. Contraction = up-stroke. Showing marked increase in peristalsis and in tonicity after addition of codein hydrochloride, 10 mgm., in 50 c.c. Locke's solution and subsequent inhibition and relaxation produced by adding 5 mgm. of narcotin hydrochloride to the same solution.

which also tends to produce constipation. (4) In the fourth place it is interesting to note that although the secretions are inhibited the absorptive power of the intestine is unimpaired. This circumstance, together with the fact that the intestinal contents are propelled more sluggishly, leads to even more complete absorption of fluid and the production of harder feces. (5) In the fifth place, according to Nothnagel,[13] Spitzer[14] and others, morphin causes an increased

[12] Cohnheim and Mordrakowski: Ztschr. f. physiol. Chem., 1911, lxxi, 273.
[13] Virchows Arch., 1882, lxxxix.   [14] Ibid., 1891, cxxiii, 593.

tone of the splanchnic nerve centers, and hence a greater inhibition of the intestinal movements. (6) Lastly, it is claimed by some authors that morphin tends to benumb or paralyze the sensory nerve-endings in the intestinal walls and thus render it still more less responsive to stimuli. [15] [16]

It is thus seen that while the action of morphin on the Auerbach and Meissner plexuses tends to stimulate the intestinal contractions, some of its other effects on the intestine tend to counteract this stimulation and inhibit the contraction and still other effects by producing changes in the consistency of the feces, tend still further to lead to constipation. The final effect is a resultant of all the factors above mentioned and depends on which of them have the upper hand or the predominating influence. This varies in different animals. Thus in cats and dogs, morphin ordinarily produces purgation. In man the result may be constipation, but very often the peripheral stimulating action is sufficient to prevent it. Again, it is well known that morphin fiends suffer alternately from obstinate constipation and frightful diarrhea.

Turning now to the benzylisoquinolin group of opium alkaloids, of which papaverin is the chief representative, we find that their peripheral effect is very different from that of the morphin group just considered. The Viennese investigator Pal[17] has called attention to the peculiar properties of papaverin, and this drug has been still further investigated by Popper[18] and by the present author.[19] Papaverin has the interesting and remarkable faculty of producing an inhibition of the contractions and relaxation of the tonus in all kinds of smooth-muscle structures. Thus it has been shown to produce a complete relaxation and marked inhibition of movements of the intestinal muscle, and that both in isolated preparations and in the intact body (Fig. 3) a similar effect, differing only in degree, is produced by the other benzylisoquinolin alkaloids narcotin and narcein (Fig. 2). Furthermore, it has been shown by Popper and others that the inhibitory effect of papaverin follows minute quantities of the drug and that small doses of that alkaloid are sufficient to counteract the tonic and stimulating effects of much larger doses of morphin. Still further it has been pointed out by the present author in conjunction with Johnson and Bollinger[20] that papaverin has a marked local benumbing or analgesic effect upon sensory nerve terminals of the skin and mucous membranes, and it is justifiable to assume that the same effect may be produced upon the sensory nerve-endings of the intestinal wall.

[15] Jacobi: Arch. f. exp. Path. u. Pharmakol., 1891, xxix, 171.
[16] Pohl: Ibid., 1894, xxxiv, 86.
[17] Zentralbl. f. Physiol., 1902, 68.
[18] Pflüger's Arch., 1913, cliii.
[19] Macht: Arch. Int. Med., 1916, xvii, 786.
[20] Jour. Pharmacol. and Exper. Therap., 1916, viii, 451.

The fact that small doses of papaverin and narcotin are sufficient to counteract the stimulating action of morphin and codein explains the empirical observation of some careful clinicians that opium is more constipating than morphin.[21]   Experiments made by the author

Fig. 3.—Jejunum of cat. Showing normal rhythmic contraction. Contraction = up-stroke. Effect of 2 mgm. of papaverin hydrochloride in 50 c.c. Locke's solution. Note marked relaxation of tonus and inhibition of contractions.
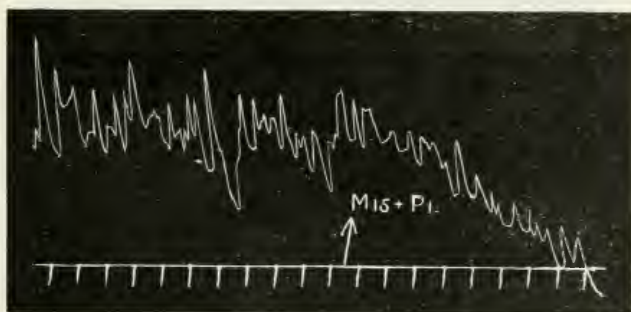
Fig. 4.—Ileum of cat.   Contraction = up-stroke.   Showing the antagonistic effects of a mixture of morphin sulphate, 15 mgm., and papaverin hydrochloride, 1 mgm., on the same preparation.   The inhibitory effect predominates.

with pantopon, a combination which contains 50 per cent. of morphin, proved that it possessed enough of the isoquinolin derivatives to

21 Fronmüller: Loc. cit.

produce an inhibition of the bowel in place of the ordinary stimulation following morphin alone (Figs. 4 and 5). If we bear in mind
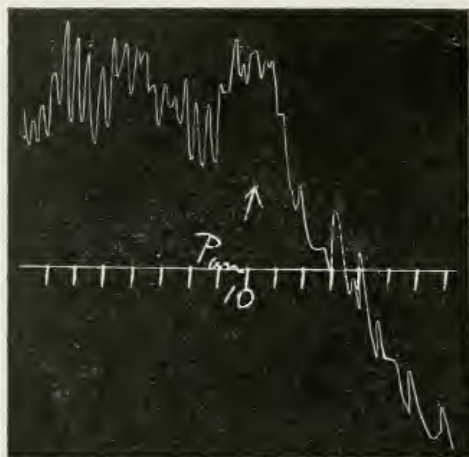
Fig. 5.—Ileum of cat. Contraction = up-stroke. Showing effect of pantopon, 10 mgm., in 50 c.c. Locke's solution.
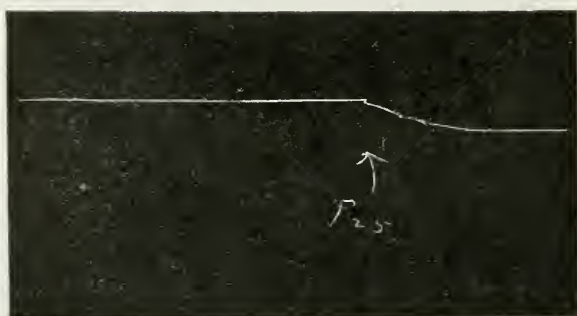
Fig. 6.—Isolated pyloric sphincter of cat. Showing relaxation after papaverin, 25 mgm., in 100 c.c. Locke's solution.
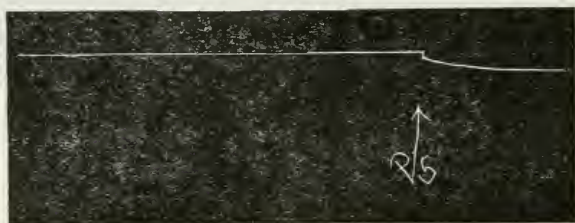
Fig. 7.—Ileocecal sphincter of cat. Showing relaxation produced by papaverin, 15 mgm., in 50 c.c.

that crude opium in addition to the various isoquinolin derivatives also contains various inert bodies such as gums and the resins, etc., it is clear that it is even more constipating than a combination of the pure total alkaloids alone.

Thus, as a result of careful pharmacological investigations, it is evident that morphin and opium possess very different therapeutic values in respect to their effect on the intestinal movements.

ACTION ON THE PYLORIC SPHINCTER. It may be well to devote a paragraph to the action of some opium alkaloids, and especially of papaverin, on the pyloric valve or sphincter, in view of their possible therapeutic applications. The spasmodic effect of morphin has already been sufficiently described.. The effect of papaverin on the pyloric sphincter is a diametrically opposite one. Roentgen-ray studies have shown that papaverin produces relaxation of the pylorus. The same has been confirmed by the present author in experiments on the isolated pyloric ring (Fig. 6) and the ileocecal sphincter (Fig. 7). Holzknecht and Sgalitzer[22] have suggested injections of papaverin in differential diagnosis of functional and organic spasm of the pylorus. Again, Delprat[23] injects papaverin for the relief of pylorospasm in infants. In connection with a study of the effects of papaverin on the ureter and other smooth-muscle tissues *in vitro* it occurred to the author to suggest its use by mouth in infantile spasm of the pylorus. Inasmuch as the toxicity of papaverin is very low, such a procedure was deemed not to be dangerous. Accordingly, solutions of papaverin-hydrochloride have been administered to infants with pylorospasm in a few cases through a stomach-tube with very encouraging results.

RENAL INFECTION.[1]

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AT the outset we confess to have accomplished nothing more important than the reduction to something like a satisfactory working basis of our sometime inapt conception of this subject.

In common with many others, we have been depressed by the enormous extent and wondrous complexity of the literature to which we are now perhaps contributing a further burden. However, a careful compilation and consultation of our own experience, taken

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[22] München. med. Wchnschr., 1913, iii.

[23] Nederl. Tijdschr. v. Geneesk, 1915, ii, 1311.

[1] Read before the Tri-State Medical Society of Virginia and the Carolinas at Durham, N. C., February 21–22, 1917.

in conjunction with a review of certain selected portions of this litera-
ture, have gradually evolved conclusions of some definiteness which
it may be worth while recording briefly.   In a series of 125 cases sub-
jected to cystoscopic diagnosis during the past two years about 30,
or 24 per cent., were found to have extrarenal causes for the urinary
symptoms presenting, and these, of course, are immediately excluded
from the present consideration.   Of the remainder, 60, or 63 per
cent. of the true urinary group, were cases of renal infection of the
non-tuberculous type.   To this number are added, for general con-
sideration, about 20 other cases in which the presence of renal
infection was so evident as not to require cystoscopic diagnosis,
and in which, for one reason or another, it was found inadvisable
or impossible to employ the accepted methods of cystoscopic treat-
ment.   Thus, in a grand total of 115 urinary cases constituting the
basis of this report, 80 were cases of non-tuberculous renal infection,
presenting an incidence of nearly 70 per cent.

GENERAL CONSIDERATION.   It would appear that the chief
cause of the disastrous confusion pervading the literature lies in
two errors: (1) The attempt to erect into distinct clinical and
pathological entities, conditions which are most probably consecu-
tive events in the same general process.   (2) The assumption that
the character of the organism involved has no determining influence
upon the course pursued by this general process in a given instance.

Certainly, the picture has unfolded with greater clarity for us,
and we have been able more intelligently to estimate our own cases
since we have come to realize: (1) that the commonly accepted
differentiations (pyelitis, pyelonephritis, pyonephrosis, perinephritic
abscess, etc.) in reality represent initial, concurrent, or terminal
stages of a general process (renal infection); (2) that the nature of
the involved organism as between the pyogenic cocci on the one side
and the ubiquitous colon bacillus on the other has a profound influ-
ence upon pathology, symptomatology, and treatment.

In reference to the former there has been a gradual swing of
sentiment in this direction in the last few years; as to the latter,
it has been extremely interesting to note, running through the recent
literature, a skein representing a true conception of the situation
by a very few, and, by a few others, a clinical and therapeutic
differentiation with an apparent lack of understanding of the
pathological basis therefor.   Most recently of all, Cabot and
Crabtree[2] have presented a report which, though of no striking
originality, is, in our judgment, of monumental importance in that
it gathers into a coherent whole the scattered threads of this skein
and surrounds it with a framework of case summaries representing
investigative work of a very high order.

Briefly stated, this new conception of kidney infection assumes,

[2] Surg., Gynec. and Obst., November, 1916.

on what appears to be sufficient evidence, that in the ordinary case the involvement begins primarily in the substance of the organ, including the pelvis and perinephritic tissue secondarily, if at all, so that a simple pyelitis rarely, if ever, exists without at some stage an inclusion of the parenchyma, though the same cannot be said of perinephritic abscess, which may at times be of entirely extra-urinary origin. The bacteriology concerns essentially the pyogenic coccus group on the one side and the typhoid colon group on the other. In the first named the process is more or less limited to the kidney itself, involving the pelvis little if at all; the lesions here are cortical abscesses, septic infarcts, diffuse suppuration, capsulitis, capsular abscess, and perinephritic abscess. In the typhoid colon group, on the contrary, the tendency is distinctly toward an attack on the convoluted tubules and the pelvis, and the lesion is a pyelonephritis which in some cases is so predominantly associated with the pelvis as to amount in clinical significance, if not in pathological accuracy, to a "pyelitis" pure and simple. The essential point in the entire consideration is the fact that the coccus has a strong inclination to abscess production and the colon bacillus none at all, though a pyonephrosis may easily (and necessarily) result from a bacillary infection if a ureteral obstruction becomes at any time added to the picture.

Etiology. Considering the etiology, we are compelled by our experience to discard, at least in part, the time-honored generality that renal infection is dependent upon an antecedent focus of infection and a kidney whose resistance has been lowered by such predisposing factors as stone, traumatism, obstruction, new growth, mobility, etc. The necessity of a bacterium is, of course, evident and the germ unquestionably comes from a preëxisting focus elsewhere in the body. This focus may be a tooth, a tonsil, a furuncle, the gall-bladder, the appendix, the intestine at large, etc.; in the majority of instances we can merely assume its existence without being able to determine its location.

The other half of the generality does not hold up so well.

In determining the occurrence of infection, predisposing factors of the types noted are of very great importance when they are present, but in a very high proportion of cases they are entirely absent. In our series this factor entered into the situation in only 35 per cent. of cases. In the others the nature of the predisposing element was as obscure as the identity of the antecedent focus. Very probably the common determining factors are less often the gross lesions enumerated above and more often the impalpable influences associated with lowered systemic resistance in general, chronic toxemias (particularly from the intestinal tract), the virulence of the particular strain of germ involved, the number of organisms reaching the kidney, and the duration of their travel kidneyward.

In this connection we call attention to several important considerations. The kidney is an excretory organ for bacteria comparable to the liver. Germs are probably being constantly fed into the blood stream from various sources and carried to these organs for elimination. It is possible for this elimination to occur without any damage to the kidney itself. We have recovered pure cultures of pneumococci from the urine of a pneumonia patient who had no renal involvement. Numerous other such cases have been reported. Rosenow has shown, however, that germs lurking in infected areas may from time to time undergo modification and acquire hitherto unpossessed selective affinities for certain structures including the kidney. Such a germ feeding into the blood stream would no longer harmlessly pass the kidney. On the contrary, it would here find its new elective localization and fall upon it. Thus, so far as organisms are concerned, they may be immediately of such high virulence as to infect the kidney promptly; they may be of a lower grade of virulence, but in such massive number as to have essentially the same effect: they may be of such a type as to fall an easy prey to the physiological activity of the kidney and do no harm; or, finally, they may originally have been of this latter class, but subsequently have developed selective destructive powers against the kidney. The germs with which we have dealt in our series are in 54 per cent. of the bacteriologically differentiated cases colon bacilli and in 30 per cent. staphylococci and streptococci. There were 16 per cent. of mixed infections, and evidence in many indicating that the colon bacillus was a secondary offender. In reference to the predisposing resistance—lowering factors, the outstanding feature, apart from the minority of gross lesions already mentioned, was chronic constipation, which with its accompanying toxemia was present in such a high percentage of cases as to demand very serious consideration. In quite a large number of cases no predisposing factor whatsoever was evident.

As to the avenue traveled by the organism in its journey to the kidney, the discussion is already voluminous enough and heated enough to make it unnecessary for us to add another word to it. We content ourselves therefore with the bare assertion that we consider the evidence:

1. Overwhelmingly against the so-called ascending infection except in a very few cases.

2. Not sufficient to identify the infection with the lymph current as a common occurrence.

3. Conclusively in support of a hematogenous route in a vast preponderance of cases.

SYMPTOMATOLOGY. Pyonephrosis is a terminal event with a symptomatology of its own which need not be considered at this time, and much the same may be said of the perinephritic abscess consecutive upon primary renal conditions. Of the latter the infec-

tions may vary from the extremely chronic to the violently acute. From the prognostic and therapeutic view-point a bacterial differentiation of the acute forms is important, and is often possible when all available diagnostic measures are employed. A coccus infection of severe grade will present high fever, chills, rapid pulse, high leukocytosis, pain on the affected side, abdominal tenderness and spasm, and a rapidly progressive toxemia. Blood cultures may show the organism. A colon infection of severe grade will present the same symptoms, though usually in lesser degree, and commonly the toxemia will not be so marked. Here also a blood culture will often prove positive. For immediate diagnostic purposes, however, consideration of the urine and function will prove of greatest value. Involving a portion of the kidney distant from the pelvis, and not particularly concerned in the elimination of phenolphthalein, a coccus infection often produces little or no change in the microscopic appearance of the urine or of the functional capacity of the kidney as measured by the dye output. So much is this true that the pronounced abdominal symptoms and the insignificant urinary findings often lure the diagnostician into an ineffective intraperitoneal operation. With bacillary infections, on the contrary, the pelvis and the convoluted tubules are primarily involved, pus, bacteria, and other pathological elements appear promptly in the urine, and the function is very profoundly affected.

The question of whether any renal infection is ever strictly unilateral is still *sub judice*. We believe the vast majority of such infections, acute and chronic, to be bilateral in spite of temporary absence of pus and bacteria from one of the kidneys. Notwithstanding this we feel convinced that there is definitely, though rarely, such a condition as an acute unilateral infection of the type described by advocates of this belief as "suppurative infarct." Furthermore, we believe that in the common bilateral acute infections the pathology is often, if not commonly, much more pronounced upon one side than the other.

We pass over the mixed infections representing the engrafting of a secondary colon infection on a primary coccus base or the reverse. Such cases, particularly when associated with gross lesions such as stone or stricture, present a complex urinary picture and a pathology still more complex. In most instances the interpretation of the picture is a matter of mere conjecture.

In the symptoms summary which follows, based on the cystoscopic series, we include both the chronic and the ordinary acute cases, excepting only the fulminating types just described. Certain cases appear to have been chronic from the outset; the usual history is an original more or less acute attack, subsidence into a mild chronic condition (often with almost complete remissions), and thereafter periodic acute or subacute outbursts. The chief characteristics noted are as follows:

Age, Sex and Race. We have wasted no time over these considerations. Renal infection is no respector of person, and occurs frequently in young and old, male and female, white and black.

Etiology. Apart from the gross accompanying lesions referred to more in detail under the head of associated conditions the etiology is often quite obscure. In 30 per cent. of our cases it was entirely undetermined, and in many others it could only be assumed. Of these latter a group constituting nearly 20 per cent. of the whole presented chronic constipation as the outstanding factor. A recent history of typhoid fever was present in 2 cases. Definite pre-existing foci were determined in 10 per cent. of cases as follows: Pyorrhea, throat infection, puerperal sepsis, operative wound infection, salpingitis, and traumatic hand infection. Reduplication of ureters was present in 3 cases, stricture of ureter in 5 cases, great mobility of kidneys in 5 cases, stone in 8 cases.

Bacteriology. The offending organism was identified in slightly over 50 per cent. of the cases. In 5 per cent. no germ could be located either by stain or culture. In the remainder the bacteriological records are incomplete, a gross error which in the future we shall attempt to avoid. Of the cases in which the germ was identified, 54 per cent. were colon infections, 30 per cent. coccus infections, and 16 per cent. mixed colon and coccus infections.

Course. The clinical duration of the lesion varied between one day and fourteen years.

Associated Conditions. In 35 per cent. of cases gross predisposing urinary lesions such as stone, stricture, and prolapse were present. In the stone cases it was often difficult or impossible to judge between cause and effect, and the same may be said of the strictures. So far as prolapse is concerned, it is interesting to note that in all cases the mobility was unilateral, but the infection bilateral except in one instance. A great variety of extra-urinary associated conditions presented themselves, mostly negligible from the etiological point of view. Pelvic complications in women were found rather often, particularly salpingitis, displacements of the uterus, and large fibroid tumors. The previous histories of the patients contained the usual citation of childhood infections, of which no particular note is taken here. Considerable significance attaches to the frequency with which these previous histories contained reference to "malaria," chronic appendicitis, and gall-stones. In several of these, long treatment, removal of the appendix, or exploration of the gall-bladder had failed to do what the ureteral catheter subsequently easily accomplished.

Side Affected. In 70 per cent. of cases the infection was bilateral. The unilateral cases were either of the type known as "infarct" or presented some condition definitely interfering with the vitality of the kidney involved: solitary kidney, rudimentary third pelvis, strictured ureter, stone in pelvis or ureter, mobility with kink of

ureter. We are inclined to question the existence of a unilateral infection exclusive of these two types. No such case appeared in our series. It is important to note, however, that the infection is commonly predominant upon one side, and that its existence upon the other (where it may be entirely dormant) can often be demonstrated only after very careful microscopic and cultural examination.

Initial Symptom. This was definitely stated in 90 per cent. of cases as follows: pain, 46 per cent.; bladder disturbance, 32 per cent.; fever, 6 per cent.; vomiting, 4 per cent.; general weakness, 2 per cent.

Predominant Symptom. In about 88 per cent. it was possible to determine the predominating symptom of the attack. In a few cases two or more symptoms were given equal prominence, and this accounts for the apparent discrepancy in the percentages: pain, 60 per cent.; bladder disturbance, 15 per cent.; fever, 10 per cent.; malaise, 10 per cent.; vomiting, 2 per cent.

Bladder Disturbance. Frequency of urination was present in 81 per cent. of cases and painful urination in 66 per cent. Combining the two a total of 86 per cent. of cases presented bladder disturbance of some kind and degree, occasionally slight but usually quite marked.

Pain. In our cases this presented a definitely higher incidence than that observed by many others, and it is in fact one of the outstanding features of the symptomatology. It was present in 77 per cent. of cases, and varied from a dull ache to a seizure of such severity as to require morphin. The pain was commonly located in the lumbar region, but sometimes appeared over the bladder, throughout the entire abdomen, under the costal arches, in the inguinal regions, and across the sacrum. It is interesting to note that it was commonly unilateral in spite of the fact that in many cases the urine of the opposite side showed findings of equal, sometimes greater, significance. The same thing may be said of local tenderness, which was found in 60 per cent. of cases.

Fever and Chills. A definite history was obtained in 54 per cent. of cases.

Gastro-intestinal Disturbances. Gastro-intestinal disturbances were present in 43 per cent. of cases.

Malaise. This was noted in 40 per cent.; in about 25 per cent. definite loss of weight was complained of.

Pyuria. This was absent in but 1 case, a perinephritic infection apparently originating in a kidney lesion without pelvic outlet. The amount of pus present varied enormously and offered no constant indication of the gravity of the process. Some of the most stubborn of the cases showed but small amounts. The findings were bilateral except as noted under "side affected," but commonly there was considerable difference in the two sides. We observed with interest that many cases which at first appeared unilateral eventually developed pus and positive cultures on the other side.

Hematuria. Blood was present in the urine in sufficient quantity to be seen by the patient in 10 per cent. of cases. No attempt was made to compile the microscopic findings.

Leukocytosis. In the more acute stages there may be leukocytosis of varying degree. Septic infarcts commonly produce a high total leukocyte and polynuclear count. In the chronic cases it is distinctly unusual to find any blood reaction. Furthermore, it is important to note that in a certain percentage of acute cases there will be no blood change. We have witnessed an initial attack with chills, malaise, temperature of 103°, and a normal leukocyte and differential count.

Function. In something over one-third of the cases separate function test was done with phenolphthalein as an indicator. In common with the experience of others our results here have been somewhat confusing, and we are more and more impressed with the importance of a careful consideration of the clinical aspects of the case before placing too great a reliance upon the dye tests in the chronic cases. In several instances the pathological condition has been accurately pictured by the indicator, a low or absent reading suggesting the nephrectomy subsequently done, with a classical compensation on the opposite side. At other times, however, very low readings have meant nothing more than the presence of a stone or some other disturbing element which did not essentially involve the parenchyma, and the removal of which would permit prompt return of the function to normal. As it is often impossible to separate these two types clinically, direct inspection of the interior of the kidney at the time of operation is the only safe guide to nephrectomy. In a very few cases we have found higher function on the affected side than on the other (one septic infarct and one stone kidney). However, certain modifying elements were present in both these cases. Finally, we have encountered several cases of apparent hyper-permeability to the dye in which abnormally high readings were present in spite of more or less marked lesions on one or both sides.

Cystoscopic. In 40 per cent. of cases the bladder picture was absolutely negative, and in 23 per cent. nothing further was noted than an edema or congestion of the trigone suggesting a chronic irritation. Cystitis was well marked in 20 per cent. of cases and of moderate severity in 12 per cent. of others. One cannot fail to be impressed with the remarkable ability of the bladder to resist infection in the presence of a stream of purulent and bacteria-laden urine which may have been flowing across it for years. In slightly over 40 per cent. of cases, pyelography was done with collargol or thorium, and with no bad results. This measure was of considerable value, but we could not so systematically as Braasch (though quite frequently) trace in the pelvic outline the signs of infection which we nevertheless demonstrated to be present.

TREATMENT. The question of treatment involves numerous considerations. A perinephritic abscess must, of course, be promptly drained, and, if of renal origin, subsequent investigation must determine the fate of the kidney itself. A pyonephrosis commonly requires a nephrectomy. Infected stone kidneys must be dealt with according to circumstances; some have to be excised; in others it is possible, though difficult, to remove the stone, and later on rid the pelvis of its infection by suitable cystoscopic measures. If a stricture of the ureter is associated with a pyelitis it will have to be dilated, and similarly an infection dependent upon prolapsus will necessitate nephropexy.

Cases without these gross complicating lesions present a problem to themselves. As a rule we are reluctant to adopt manipulative procedures in an acutely inflamed urinary tract, but very often we feel that no other recourse is left. The acute coccus infections often, and the acute bacillary infections rarely, reach surgical proportions. The progressive toxemia accompanying the so-called unilateral infarct or the bilateral coccus infection (with preponderance of pathology on one or the other side) may within a few days or hours imperatively demand drainage of cortical abscesses or even nephrectomy. We would, however, advise extreme caution lest we too hastily adopt this irrevocable measure. In many cases such kidneys have an astounding reactive ability, and the patient with almost dramatic suddenness will pass from great danger to comparative safety. Moreover, we will hereafter refuse to recommend or adopt the more radical procedures until a preliminary lavage of the pelvis has been undertaken. We are aware that in this type of infection the inaccessible cortex is chiefly involved and lavage supposed to be of questionable value. However, in several cases (two of them still under treatment) silver nitrate irrigations of the pelvis have aborted attacks which appeared to be imminently demanding nephrectomy. We regret that lack of space prevents detailed reports of these cases. In the last of the series the clinical picture was absolutely classical, including a positive staphylococcus blood culture. Should lavage fail, however, we would then unhesitatingly remove the offending kidney.

When the coccus infection is not of this fulminating type it will generally subside rather promptly, though it will sometimes pass over into a chronic condition. The acute colon bacillus infections will rarely at any time require operative measures; the toxemia here is usually less severe, but there is a much greater tendency of the infection to relapse into the chronic with periodic acute exacerbations. Treatment of the chronic infections and of these latter acute forms may be considered under the same terms. Attention to diet rest, sleep, fresh air, and general hygiene are important. The most valuable internal medication consists of draughts of pure water. We cannot overestimate the importance of demanding that the

patient systematically flood the urinary tract. Antiseptic drugs have been disappointing. The formaldehyde-carrying formulas (urotropin) have a definite germicidal action in the bladder when properly used, and a similar but vastly less potent action at the level of the pelvis of the kidney. In the substance of the organ where the cocci are lodged they are of no value whatever. The ideal urinary antiseptic has yet to be found; in the meantime we would add methylene blue and quinin to the therapeutic arsenal. Vaccines, autogenous or otherwise, have not proved their case in our hands. Our judgment would instruct us, however, that this is probably less the fault of the vaccine than of our understanding of its proper application. We are rather convinced that vaccines will eventually be of much service in these conditions, and we desire to push our investigations in this direction. The remedy *par excellence* is lavage of the pelvis. We deprecate the discouraging tone of a recent publication.[3] Our experience in many cases utterly contradicts the conclusions of this writer. In his opinion kidney infections, curable through pelvic lavage, owe their recovery to catheter dislodgment of material which blocks the lumen of the ureter, and hence he believes that "the less dangerous procedure of simple ureteral catheterization" is equally efficacious. In expert hands a properly conducted lavage is without danger, and in more than 200 pelvic irrigations we have yet to meet a single one of the sequelæ mentioned in this article. Obstructive material has not often been present in the ureter in our cases. Furthermore, in many instances in which we have practised preliminary diagnostic catheterization without lavage, but with theoretical removal of the obstruction, there has been an entire absence of the improvement which has followed later when systematic lavage was undertaken. In brief, our experience, so far as we are concerned, negatives every point advanced by this author.

For lavage we have abandoned all other media in favor of silver nitrate and formaldehyde. Of the two, silver is much the more constantly effective. The precipitate of silver chloride in the urine is disconcerting and has led us from time to time to search for some substitute. Invariably, however, we have been forced by clinical results to return to silver. We have failed to note, however, that the higher percentages (5 per cent.) are of any greater effect than the lower (1 per cent.).

It must be remembered that in spite of all treatment, including lavage, some infections will prove ineradicably rooted in the pelvis. Temporary improvement can often be effected in these cases, and by periodic séances the condition can be held more or less constantly in leash; but a permanent complete cure appears hopeless unless nephrectomy is undertaken.

[3] Surg., Gynec. and Obst., January, 1917.

BANTI'S DISEASE.

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For years clinicians have used the term splenic anemia to designate a condition manifested by splenomegaly and by anemia supposedly due to disturbances in the spleen. The term was long made to cover a conglomeration of anatomical lesions, among them the primary splenomegaly of Gaucher, the congenital and acquired forms of hemolytic jaundice, and the so-called Banti's disease. The first two recently have been eliminated and classified elsewhere, and it is with the last named that we purpose to treat in the present communication. It will be shown, we think, that Banti's disease as an entity has no legitimate claim to recognition, and that the designation is an encumbrance in the nomenclature of splenic diseases; that it really represents a splenic manifestation of syphilis usually with, but occasionally without, concomitant sclerotic changes in the liver, and that all the clinical and anatomical requirements of the disease as originally postulated by Banti are adequately satisfied by syphilis.

Banti's disease, according to the original description of the Italian pathologist,[1] is divisible into three symptomatic stages, namely, the pre-ascitic, the intermediary, and the ascitic. The pre-ascitic stage is inaugurated by insidious hyperplasia of the spleen, the organ commonly reaching several centimeters below the level of the costal slope before the enlargement is detected, by diminution in the number and in the hemoglobin content of the red cells, and by poikilocytosis and microcythemia, but without changes in the number or in the ratio of the white cells. At this stage exploration of the abdomen reveals a markedly enlarged spleen and a liver that is perfectly smooth or slightly irregular in contour, the sclerotic changes being limited in extent and so distributed as not to interfere with the portal circulation. The intermediary stage is attended by digestive disturbances dependent

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[1] Banti: Semaine Méd., July 11, 1914, p. 318.

upon chronic passive congestion of the gastro-intestinal mucous membrane, and occasionally by hemorrhages. In the ascitic stage the abdomen fills with serous fluid, thus completing the cycle of portal obstruction, jaundice may or may not be present, emaciation and anemia are extreme, and death supervenes. Autopsy reveals enlargement of the spleen to the extent of from 500 to 1200 gm. or more, and the liver is cirrhotic.

While Banti's exposition constitutes a straightforward description of what he undoubtedly believed to be a distinct disease, it is none the less a confusing contribution to the subject of splenic pathology, and, to confound matters still further, Osler,[2] in this country, stood sponsor for Banti's views in a paper founded almost exclusively on clinical observations, thus helping to perpetuate error in regard to a subject already hopelessly involved and based on an insecure anatomical foundation. Others still more boldly included under the caption of Banti's disease such lesions as traumatic thrombosis of the portal vein and its tributaries attended by secondary splenomegaly,[3] enlargement of the spleen associated with patency of the umbilical vein,[4] etc.

Syphilis as a factor in Banti's syndrome has received consideration in isolated instances only. For example, in a syphilitic spleen Marchand[5] found histological changes identical with those described by Banti, and advanced the view that many cases of so-called Banti's disease may be due to preservation of a congenital syphilitic splenomegaly. In a case reported by Coupland[6] the clinical features were typical of Banti's disease, but operation for removal of the spleen revealed the gnarled liver of syphilis. In the case reports of three operations for splenectomy in syphilitic subjects Giffin[7] has drawn an entirely acceptable picture of Banti's disease, and similar cases have been recorded from time to time by Hartwell,[8] French and Turner,[9] Osler,[10] Anderson,[11] Caussade and Levi-Franckel,[12] Queyrat,[13] and Hochhaus.[14] As far as we have been able to learn, however, there has been no systematic attempt to establish a relationship between syphilis and Banti's disease.

Enlargement of the spleen, exclusive of the gummatous variety, is not an uncommon event in syphilis, and occurs both in the con-

[2] Osler: Am. Jour. Med. Sc., 1902, cxxiv, 751.
[3] Heller: Verhandl. d. deutsch. path. Gesellsch., Jena, 1904, p. 182.
[4] Baumgarten: Arbeit. aus dem path. Instit. zu Tübingen, Leipzig, 1907, vi, 93.
[5] Marchand: München. med. Wchnschr., 1903, I, 463.
[6] Coupland: British Med. Jour., 1896, i, 1445.
[7] Giffin: Am. Jour. Med. Sc., July, 1916, p. 5.
[8] Hartwell: Med. Record, March 28, 1914, p. 593.
[9] French and Turner: Proc. Royal Soc. Med., 1913–14, vii, 77.
[10] Osler: Clinical Jour., 1914, xliii, 462.
[11] Anderson: Canada Lancet, 1914, xlvii, 740.
[12] Caussade and Levi-Franckel: Bull. et mém. Soc. méd. des hôp. de Paris, 1914, xxxvii, 1029.
[13] Queyrat: Ibid., 1914, xxviii, 296.
[14] Hochhaus: München. med. Wchnschr., 1904, li, 1410.

genital and acquired disease.   In a study of 348 cases of spleno-
megaly in children, Carpenter[15] found 57 cases in congenitally
syphilitic subjects, syphilis, as a cause of splenomegaly and anemia,
ranking second only to rickets, of which there were 60 cases.   The
clinical indications were those of the so-called anemia infantum
pseudoleukemica of von Jaksch.   That the syphilitic splenomegaly
of childhood may persist is suggested by its frequent association
with syphilitic cirrhosis—hepar lobatum—in the deferred congenital
syphilis of young adults.

In the early stages of acquired syphilis in adults the spleen is
palpably enlarged in about one-third of all cases, but the enlarge-
ment is to be ascribed in great measure to participation of the
splenic follicles in the general lymphoid hyperplasia by which this
period of infection is attended.[16]   The spleen in the later stages of
acquired syphilis, however, may show inflammatory overgrowth of
connective tissue to such an extent as to constitute the chief factor
in an enlargement which may attain proportions second only to
the splenomegaly of Gaucher and of myelogenous leukemia.   More-
over, the syphilitic splenomegaly in question may exist quite inde-
pendently of cirrhotic changes in the liver, and, in certain instances,
it combines with anemia to fulfil the essential requirements of the
first, or pre-ascitic stage of Banti's disease, in which symptoms
referable to disturbances in the liver are conspicuous by their
absence.   Thus in one of Giffin's cases[17] the patient was a woman,
aged forty years, who stated that her spleen had been enlarged for
twelve years.   There was a marked anemia of the secondary type.
At operation it was observed that the liver was smooth.   The
spleen was removed, and measured 30 x 17 cm. and weighed 900
gm.   Microscopic examination showed the presence of a diffuse
fibrosis corresponding to that described by Banti, together with
numerous spirochetes in the walls of the splenic vessels.   In the
autopsy room at Bellevue Hospital we have several times noted
the presence of splenomegaly in syphilitic subjects without atten-
dant cirrhotic changes in the liver, while the association of anemia
and splenomegaly with the scarred and coarsely lobulated liver of
syphilis is one of the commonest and most characteristic combina-
tions encountered in luetic subjects, frequently presenting a clini-
cal picture indistinguishable from that of Laennec's cirrhosis, with
which, indeed, and the later stages of the so-called Banti's disease
it often is confounded.   Thus in 50 cases of hepar lobatum exhib-
ited among 4880 autopsies at Bellevue Hospital, 32, or 64 per cent.,
were accompanied by enlargement of the spleen,[18] and of 17 cases
in which the weight of the spleen was recorded, the average was

[15] Carpenter: Brit. Med. Jour., 1903, ii, 463.
[16] Douglas Symmers: Am. Jour. Med. Sc., December, 1910, p. 859.
[17] Giffin: Loc. cit.
[18] Douglas Symmers: Jour. Am. Med. Assn., 1916, lxvi, 1457.

634 gm., or 434 gm. in excess of the extreme normal weight of 200 gm., and in 65 per cent. of the cases the enlargement was dependent upon diffuse overgrowth of connective tissue. The individual weights were 275, 300, 420, 440, 460, 500, 530, 540, 600, 620, 630, 730, 750, 800, 840, 980 and 1340 gm.

Of 24 cases of Laennec's atrophic cirrhosis of the liver occurring in syphilitic subjects the spleen was described as enlarged in 6 cases, in 8 cases the size was not indicated, and in 10 cases the weights were, respectively, 270, 370, 400, 500, 500, 500, 620, 730, 740 and 1300 gm., giving an average of 593 gm., or 393 gm. in excess of the extreme normal weight. However, in 17 cases of atrophic cirrhosis occurring in non-syphilitic subjects the average weight of the spleen exceeded the extreme normal limit by only 112 gm.

The tendency of syphilis is to pursue a course marked by inflammatory changes resulting in overproduction of connective tissue. In no organ is the inimical effect more pronounced than in the liver, in which sclerotic changes are frequently ascribable to syphilis. In atrophic cirrhosis, however, the cause most often invoked is, of course, alcohol. Nevertheless, of 84 frank examples of Laennec's cirrhosis encountered among 4880 autopsies at Bellevue Hospital there were definite syphilitic lesions in other organs in 24, or in 28.5 per cent., distributed thus: syphilitic aortitis 12, chronic interstitial orchitis 11, indurative atrophy of the base of the tongue 5, pigmented atrophic pretibial scars 4, stenosis of the rectum and penile scarring one each. In this connection it is of moment to recall that of all recent cases diagnosed clinically in Bellevue Hospital as atrophic cirrhosis of the liver the Wassermann reaction with the cholesterin antigen was positive in about 80 per cent., and in a number of these cases the diagnosis was confirmed by postmortem examination. The facts in question, considered in connection with the known tendency of syphilis to induce sclerosis of connective tissue, and the peculiar susceptibility of the liver, show that syphilis, even when acting alone, is a powerful factor in the etiology of atrophic cirrhosis of the liver, and that when coupled with the destructive effects of alcohol on the liver cells themselves its potency in the matter of stimulating the production of connective tissue is still further increased.

Of that variety of cirrhosis of the liver in which syphilis is universally recognized as the sole exciting cause, namely, the so-called hepar lobatum, 50 cases were encountered among 314 syphilitic subjects coming to autopsy in Bellevue Hospital. The lesion occurred oftenest between the ages of twenty and fifty years. In half of the cases there were definite anatomical lesions of syphilis in other parts, particularly in the skin, the visible mucous membranes, and the osseous system. The spleen was described as enlarged, considerably enlarged, or greatly enlarged in 32 cases, or in 70 per cent.

In a number of cases the postmortem discovery of syphilitic changes in the liver was purely accidental, just as autopsy commonly reveals well-marked examples of atrophic cirrhosis in subjects in whom, during life, there was not the slightest reason to suspect changes in the liver. In 30 of the 50 cases of hepar lobatum, however, it was possible to secure a clinical history, and, of this number, 15 admitted infection by syphilis, or presented a suspicious history of contamination.

In 18 of the cases (or 60 per cent.) the liver was palpated during life and in 9 cases the spleen was felt. Twelve of the patients were jaundiced, in 15 ascites was present, in 9 there were subcutaneous varices, and hemorrhoids in 7. Fourteen patients gave a history of frequent vomiting, and in 7 hematemesis had occurred. Pain or tenderness in the abdomen occurred in 23 and was referred to the region of the liver 11 times. In 8 of the 23 patients the abdominal pain was the chief and most persistent complaint. Secondary anemia was present in 11. In short, the clinical composite in syphilitic cirrhosis of the liver, whether of the hob-nail or coarsely lobulated type, is an absolute counterfeit of that formulated by Banti for the intermediary and ascitic stage of the disease described by him as an independent entity.

The blood picture in syphilis varies from that of an anemia of the chlorotic type, observed oftenest in the active stages, to one of the pernicious variety occurring in the late secondary and tertiary periods. Anemia of the simple secondary sort is exceedingly common. Banti contended that the splenomegaly in the disease described by him was the primary lesion, and that the spleen elaborated toxic substances which not only caused the anemia, but were also productive of the cirrhotic changes in the liver. In support of this he maintained that splenectomy is not uncommonly followed by relief of anemia, and cited cases operated upon by Spencer Wells, Czerney, Pean and others. Certain of Banti's followers went further and claimed that if splenectomy were done not only did the anemia disappear, but the cirrhotic changes in the liver did not arise or, if already present, ceased to progress or even disappeared! The sophistry of this method of reasoning is too patent to merit discussion. It is true that in certain cases removal of the spleen is followed by improvement. In the same way splenectomy in both the congenital and acquired forms of hemolytic jaundice is often followed by complete and permanent dissipation of the jaundice and by disappearance of the changes in the blood. In the splenomegaly of syphilis there is likewise evidence to show that splenectomy is commonly succeeded by relief of mechanical symptoms as well as of disturbances in the circulation, and that the anemia is apt to undergo marked improvement or to disappear entirely.[19]

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[19] Coupland, Hartwell, Giffin: Loc. cit.

According to Banti the histological changes in the spleen in the disease described by him are characteristic, and are attended by thickening of the capsule, by diffuse overgrowth of the interstitial connective tissues, and by sclerosis of the Malpighian follicles. In the course of numerous histological investigations of the spleno-megaly of syphilis we have invariably encountered identical altera-tions. Moreover, sclerosis of the follicles, to which Banti and his adherents attach great significance, is one of the commonest changes to be observed in the lymphoid tissues of the spleen and in the germinal centers of the lymph nodes throughout the body in cases of recessive status lymphaticus. It is a well-established fact that sudden death in subjects of status lymphaticus is attended by wide-spread necrosis of the germinal follicles in the spleen and lymph nodes.[20] It is equally well recognized that subjects of status lymphaticus often survive the peril of sudden death despite numer-ous intervals of intoxication resulting in necrosis of the follicles, and that repair of the necrotic lesions is manifested by connective-tissue replacement of appearance identical with that described by Banti in the spleen. In fact, the picture is so constant and so characteristic that this finding alone justifies the diagnosis of recessive status lymphaticus—an opinion which we have confirmed on occasions too numerous to permit of any doubt as to its accuracy.

CONCLUSIONS. 1. The so-called Banti's disease is neither an inde-pendent clinical nor anatomical entity, and the designation should be eliminated from the nomenclature of splenic pathology, since it not only carries with it the objections customarily urged against the surnamed diseases, but is in reality a manifestation of visceral syphilis. This conclusion is based on the following facts:

(a) The later stages of acquired syphilis are occasionally attended by enlargement of the spleen arising absolutely independently of cirrhotic changes in the liver, and, when combined with the sec-ondary anemia so constantly to be observed in the syphilitic, it fulfils the essential requirements of the first, or pre-ascitic stage of Banti's disease as originally postulated.

(b) In other cases of late acquired syphilis splenomegaly and cirrhosis of the liver are combined, in which event jaundice, subcu-taneous and submucous varices, ascites, digestive disturbances dependent upon chronic passive congestion of the gastro-intestinal mucous membrane, hematemesis, and related changes constitute an exact clinical counterpart of the picture given by Banti for the intermediary and final stages of the disease described by him.

(c) The syphilitic cirrhosis of the liver just referred to is of two varieties, one corresponding to the atrophic or hob-nail liver of Laennec, in which syphilis is an etiological factor in at least one-

[20] Blumer: Johns Hopkins Hosp. Bull., October, 1903, p. 271.

third of all cases; the other, the coarsely lobulated liver (hepar lobatum), in which syphilis is universally recognized as the specific cause.

(*d*) In 4880 autopsies at Bellevue Hospital cirrhosis of the liver occurred 74 times in 314 luetic subjects, or in 23.4 per cent., and of this number there was an associated splenomegaly of marked proportions in 48, or 64.8 per cent. Of the 74 cases, 50 were of the coarsely lobulated type and 24 of the atrophic or hob-nail variety.

2. The histological changes in the spleen in the condition described by Banti are identical with those due to syphilis. The lesion is a chronic diffuse interstitial splenitis attended, in certain instances, by sclerosis of the Malpighian follicles. Banti and his followers attach great significance to the latter finding. As a matter of fact, sclerosis of the Malpighian follicles is characteristic only of recessive status lymphaticus, in which it occurs with almost unfailing regularity, and in the spleen of the so-called Banti's disease it is but a coincident histological change.

REVIEWS

The Roentgen Diagnosis of Diseases of the Alimentary Canal. By Russell D. Carman, M.D., Head of Section on Roentgenology, Division of Medicine, Mayo Clinic, and Albert Miller, M.D., First Assistant in Roentgenology at the Mayo Clinic. Pp. 558; 504 original illustrations. Philadelphia and London: W. B. Saunders Company, 1917.

The authors of this book are widely known by their writings and by professional reputation throughout the medical profession, as well as among roentgenologists, and their efforts in presenting this work should be duly rewarded by the just praise they have earned and deserve. It is a most valuable text-book for the beginner in roentgenology and reference work for the roentgen specialist, and it cannot fail to be of frequent use to those practising other branches of the profession. The book covers the entire subject of the roentgen diagnosis of those conditions of the alimentary canal in which this method is applicable. Very few pages are devoted to apparatus, as this is really foreign to the subject. The text is concise and clear and the illustrations are excellent, and have been well chosen from the wealth of material upon which the authors have had opportunity to draw. Truly, this is a book of which we Americans have reason to be proud. The conditions of the alimentary tract that are within the scope of roentgen diagnoses are so numerous that space forbids making more than the general statement that all of them have been included. In many instances reproductions of the pathological specimens accompany those of the lesions as shown roentgenographically. The bibliography accompanying each section shows well the use the authors have made of literature and is an important feature that will appeal to the roentgenologist using the book for reference. Careful attention is given to technic, first in a chapter dealing with this subject generally, and then in connection with the examination of each portion of the tract. The roentgenographic and roentgenoscopic signs of each condition are clearly described. These are features that must appeal to the student or beginner who lacks experience. Finally, a perusal of this book cannot do otherwise than convince the surgeon and the internist of the undoubted value of this aspect of roentgen diagnosis in skilful hands and its utter uselessness in those of the inexperienced. H. K. P.

Asthma: Presenting an Exposition of the Non-passive Expira-
tion Theory. By Orville Harry Brown, A.B., M.D., Ph.D.,
formerly Assistant Professor of Medicine, St. Louis University.
With a Foreword by George Dock, Sc.D., M.D., Professor of
Medicine, Washington University Medical School, St. Louis.
36 engravings. St. Louis: C. V. Mosby Company, 1917.

Dr. Brown has produced an interesting monograph, but one
which we find more interesting than convincing. The book is offered
as a substantiation of his theory of "non-passive expiration" as
the cause of asthma. Briefly stated, this theory is that prolonged
forcible expiration interferes with the flow of blood and lymph
in the thorax, causing a congested, edematous condition of the
mucous membrane. The consequent swelling of the mucosa
obstructs the passage of air through the bronchi, which gives rise
to the characteristic dyspnea. Among the varieties of violent
expiratory efforts which may cause this stagnation in the bronchial
mucosa he lays special stress on coughing.

In support of this theory he describes in some detail the anatomy
and physiology of the respiratory tract, various historical data, his
own observations of the paroxysms, and the results of certain thera-
peutic measures. He has, however, an annoying habit of disregard-
ing any physiological or clinical facts not in harmony with his
theory. For example, one should imagine that if violent expiratory
efforts were the important causative factor, asthma would occur
very frequently after whooping-cough. The only explanation he
has to offer as to why all coughs do not lead to asthma is that
the production of this symptom "will depend upon several factors
—namely: (1) the force, the duration, and the repetitions of the
forceful expirations; (2) the strength of the walls of the vessels
in the bronchial mucosa; (3) the extent, character, and severity of
the bronchitis; (4) the strength of the right heart or its ability to
withstand the increased pulmonary blood-pressure; (5) the natural
resistance and resilience of the tissues; (6) the extent to which the
expiration collapses or flattens the thin-walled bronchioles." One
should think that a coughing paroxysm severe enough to rupture
bloodvessels in the eye, as frequently occurs in whooping-cough,
ought to overcome the resistance of the vessels of bronchial mucous
membrane. He ascribes the beneficial action of morphin to its
retarding influence on respiration, but offers no word as to the
modus operandi of atropin; while the beneficial effects from burn-
ing the various "asthma powders" he attributes "largely, if not
entirely, to the slow complete inhalation and deliberate, prolonged
expiration."

In the treatment of asthma he recommends that during the
attack either a combination of morphin and strychnin or adrenalin
be given, but lays special emphasis on proper breathing. The

patient should be urged to exhale slowly and to restrain, so far as possible the desire to cough. In the interval respiratory exercises should be given and the general health built up. He believes that a large proportion of asthmatics are tuberculous.

The book shows an extraordinary industry in the search of the literature, over 500 authors being quoted. These citations would have been more useful if they had been in some way correlated; a simple jumble of what Smith, Jones or Robinson has recommended makes tiresome reading. Despite, however, Dr. Brown's laborious investigations, we are not convinced that the mystery of asthma is as yet unraveled. H. C. W., JR.

MANUAL OF DISEASES OF THE EYE. By CHARLES H. MAY, M.D., Director and Visiting Surgeon, Eye Service, Bellevue Hospital, New York. Ninth edition. Pp. 426; 377 illustrations. New York: William Wood & Co., 1917.

THIS last edition is a careful revision of those which have already been so well received. The author has kept always in mind the original plan not to make his volume too cumbersome for student or practitioner. The more commonly met ocular conditions are well and authoritatively considered, as is proper in a work of this nature; rare conditions and theoretical discussions are given but passing notice.

The medical student who has not the time to devote to an intensive study of ophthalmology will find this treatise a most valuable work. B. F. B.

HANDBOOK OF ANATOMY. By JAMES K. YOUNG, M.D., F.A.C.S., Professor of Orthopedic Surgery, Philadelphia Polyclinic. Fifth edition. Philadelphia: F. A. Davis Company, 1917.

THAT compends of anatomy, of which the volume under review is a favorite example, are still largely used, is evidenced by the call for a new edition of this book within so few years. As a convenient means of review, or of refreshing the memory as to anatomical facts previously learned from dissection and the more elaborate text-books, compends have a legitimate role, provided that such epitomes are accurate and up to date. Depended upon, however, as the primary source of anatomical knowledge, as they too often are by students, they lamentably fail to convey an adequate understanding of the subject.

The incorporation of the Basle nomenclature (BNA) is an admirable feature of the new edition. It is to be regretted that the

spirit of the text, too, has not been modernized, and the occasional misleading descriptions, perpetuating obsolete teachings of a generation ago, had not been replaced by the newer conceptions. An illustration of this fault is seen in the table of the Cranial Nerves, in which the olfactory bulb and tract—atrophic parts of the rhinencephalon—are still regarded as the first cerebral nerve. Then in the matter of "deep origins" of the mixed cerebral nerves the student is likely to be confused by failure to distinguish between the true deep origins of efferent fibers and the reception nuclei, in which the afferent fibers end.   G. A. P.

Food for the Sick. A Manual for Physicians and Patients. By Solomon Strouse, M.D., Associate Attending Physician, Michael Reese Hospital; Professor of Medicine at the Post-Graduate School, Chicago, and Maud A. Perry, Dietitian at the Michael Reese Hospital, Chicago. Pp. 270. Philadelphia and London: W. B. Saunders Company, 1917.

This small book—intended as a practical guide for physician, nurse, family, and patient, and to overcome the so-frequent misunderstandings as to the patient's diet and to offer, in practical terms, the proper foods, the reasons for it, and its preparation—fulfils its purpose well.

After a brief chapter on food—its definition as to use, composition and value, the Atwater tables are given and examples demonstrating its usage.

The body requirements in heat units are very simply explained and illustrated. Hereupon follow, in separate chapters, diets in diseases of metabolism, of kidneys, of heart, of stomach, of intestines, of liver, of respiratory tract, of skin, in fevers, in obesity, and in anemia, scurvy, and goiter, and in each is reason for diet, point to be attained, specimen diets and how to prepare the different dishes.

Most of the diets are now in use at the Michael Reese Hospital.

It is well written, clear, and in terms easily understood by the usual patient.

To the physician it offers a ready diet and a good guide. It helps very much to fill the frequent chasm between him and patient by the definite prescribing of what to eat and how to make it. It is a good book for the family library, the sanitarium and the hospital.   J. D.

PROGRESS

OF

MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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Pyloric Obstruction in Infancy.—SCHORER (*Medicine and Surgery,*
1917, i, 541) reports a study of this subject based upon 3 cases of com-
plete obstruction and 20 cases of spasmodic or intermittent obstruction
at the pylorus. Pylorus obstructions in infancy were long overlooked,
and today there are many physicians who do not know of their existence;
and when they see them, take away their best food, mother's milk, and
put them on artificial and proprietary foods. We do not need mother's
milk for the feeding of infants, but in pyloric obstruction we can use
it to the best advantage. Recurrent projectile vomiting in infants
should always arouse suspicion of pyloric obstruction. In infants it is
of two types or different degrees of severity. In one, operative treatment
is indicated and, in the other, medical treatment is as definitely indicated.
In all cases there probably are pathological changes at the pylorus;
this in some cases progresses to being incompatible with life, in others
it comes to a stand-still or recedes. Spasm plays a part, but whether
this is physiological or functional, or merely enough to make the attacks
spasmodic, is an open question. Differentiation of the cases may not be
pertinent in the cases that come to us early, for in these cases we may
try the medical treatment first; but in the cases seen a few weeks after
onset, those in which the peristaltic waves are marked, a tumor can be
felt, the stools are scant and dark, resembling meconium; there is
retention, as shown by test meals or the x-ray observation after proper
administration of the bismuth meal, and there is constant loss of weight.
Those cases seen late in which it is difficult to bring out the peristaltic
waves, in which a tumor cannot be felt, in which there is little or no
retention, and in which there are fecal stools, may have the benefit of
medical treatment for several days or a week before operation should
be resorted to. Operation should be done, under these conditions;
vomiting and retention are not decreased, and when there is no gain in

weight even though there be no palpable tumor. While gastric lavage twice a day may be the recognized medical treatment, this practically only is possible in the hospital or in wealthy families. Removal of a patient to the hospital often deprives it of its mother's milk; therefore, if as good results can be obtained by proper feeding, the administration of bromide and belladonna with occasional washings must receive attention. The operation of Straus is the best.

Deep Palmar Infections.—BEYE (*Ann. Surg.*, 1917, lxvi, 24) made an anatomical study of the surgery of palmar infections and says that his results substantiate those of Kanavel. He emphasizes the following points: The radial and ulnar bursæ lie completely behind the flexor tendons of the wrist, and extension of infection at this level tends to produce deep cellulitis of the forearm and involvement of the wrist-joint. Under the annular ligament these bursæ lie partially anterior to the flexor tendons. Infections tend to point to the anterior surface of the wrist proximal to the ligament as well as into the carpal joints. The nerve supply to several of the thenar muscles crosses the radial bursa in the region of the distal border of the annular ligament. Intimate relationships between the bursæ and the deep spaces of the palm. Midpalmar space does not extend proximal to the distal level of the annular ligament. Infection extending toward the wrist from this space must involve the ulnar bursa. There is an intimate relationship between the midpalmar and palmar thenar spaces — the boundary between them being a thin wall of connective tissue. There is a relationship between the theca of the index finger and the lumbrical extensions of the midpalmar space. The midpalmar and palmar thenar spaces may be true bursæ, as has been shown conclusively in one case; this should be borne in mind in dealing with affections of the hand other than acute infections. It is conceivable that such conditions as acute traumatic bursitis and tuberculosis of these bursæ may occur.

Notes on Artificial Limbs for Soldiers and Sailors.—LITTLE (*Am. Jour. Orthop. Surg.*, 1917, xv, 596) says the general rule that the more can be saved, the better, remains a sound one, but there are some exceptions. In the foot, if the metatarsus is lost, Syme's amputation gives a much more useful stump than Chopart's or Pirigoff's, or any of the other tarsal amputations. In the leg the junction of the lower and middle thirds is a better site than any below it. Stumps of the lower end of the leg are often ill-nourished and the skin cyanotic and prone to break down. For similar reasons, in the forearm an amputation two inches above the wrist is better than through the wrist-joint. In the upper third of the thigh, if it is not possible to preserve at least five inches of the femur (measured from the tip of the great trochanter), it is better to exarticulate and to avoid voluminous flaps, which hinder the accurate fitting of a leather socket. A short piece of femur is not capable of controlling a bucket, but prevents a proper bearing being obtained for a "tilting table" (a stiff leather socket enabling a patient after exarticulation at the hip-joint to walk better than one who has less than six inches of the femur remaining). At the shoulder also amputation near the surgical neck of the humerus leaves a useless stump, which only hinders fixation of a shoulder-cap arm.

THERAPEUTICS

UNDER THE CHARGE OF

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Radium Therapy in Cancer.—EWING (*Jour. Am. Med. Assn.*, 1917, lxviii, 1238) says that the progress of radium therapy in cancer has been so rapid, many of its results have been so paradoxical, and the time test of their permanency so important, that it is difficult to conceive just what position radium therapy will eventually occupy. The fact that radium will bring about the destruction of tumor cells without seriously injuring the contiguous normal tissue is of great biological interest, probably the most important single contribution of modern cancer research. Ewing says that radium is only a locally acting agent, and it is difficult to see how it can be made to exert a universal action over the body as to affect the constitutional element in cancer. It is not, therefore, the ideal cancer cure which some have conceived and many demand before they will pay attention to new treatments for cancer. In the author's opinion the future position of radium is not to be merely as a palliative in advanced or recurrent cancer, in which capacity it is of great value, or as an adjuvant to surgery with which it may be used to advantage, but as an agent for dealing with certain forms of early and strictly operable cancer. At present it will be well to limit the use of radium to cases in which there is some contra-indication to operation. In regions like the tongue and buccal or pharyngeal mucosa, where operation is mutilating and highly unsatisfactory, radium certainly deserves a trial. Radium has been successfully used in the field of uterine cancer and there is more and more a tendency to extend its use to the strictly operable forms of the disease. Ewing does warn against the possible abuse of the use of radium in cases where early operation may also be advised. On the other hand, there is great hesitation and delay practised by many physicians in dealing with early lesions of doubtful nature. It is just in this field of precancerous lesions, hypertrophies, atypical inflammatory overgrowths, warts and polyps of mucocutaneous functions, numerous leukoplakias, cervical erosions, nevi, and many accessible benign tumors, that radium is both efficient and comparatively free from danger. Ewing reviews briefly the more important literature dealing with the use of radium in cancer and discusses the affect of radium on the various types of cancer from the stand-point of pathology.

The Serum Treatment of Seventy-six Cases of Epidemic Poliomyelitis.—AMOSS and CHESNEY (*Jour. Exper. Med.*, 1917, xxv, 581) report 26 cases of poliomyelitis treated with serum obtained from persons recently recovered from poliomyelitis, at which time it is supposed to contain immune substances in greatest concentration. The treatment was begun with definite plans for administering the

serum early in the disease and in large amounts. The time limit between onset and treatment was set at forty-eight hours, and of the 26 cases treated, 18 were treated within this time. Apparently the best results were obtained in cases treated within thirty hours after onset, though beneficial results were obtained in one instance as late as ninety-six hours after onset. Of 12 cases which showed paralysis at the time serum was first given, one patient died ten hours after the serum was given, 2 patients suffered some degree of extension of the paralysis, while the remaining 9 showed no extension of the paralysis. Of 14 cases in which no paralysis was detected at the time serum was administered, 2 patients developed respiratory paralysis and died; and 2 others developed some degree of weakness or partial paralysis of certain muscle groups. The 10 remaining cases (72 per cent.) never showed any detectable weakness. In the ten instances in which no paralysis occurred, the fever, sometimes high, tended to fall rapidly to normal, the average time of the fall being 25.7 hours. The authors believe that this moderate number of cases is sufficient to demonstrate the harmlessness of the serum when introduced intraspinally. The gravity method of injection was always employed. Each sample of serum was tested bacteriologically and in every instance a Wassermann test was made to exclude syphilitic taint. Particular care was taken to obtain serum free from corpuscles or hemoglobin. With attention to these details reactions to the serum treatment may be reduced to the minimum. The question of multiple and repeated injections of the serum has not yet been worked out. In the cases here reported and especially in the group in which no paralysis existed at the time of the first injection, the pathological process either did not progress at all, or where there was extension, as in two cases the upper segment of the spinal cord became rapidly involved, and was followed by respiratory paralysis and death. Probably in cases in which some degree of muscular weakness develops soon after the injection of serum, reinjection twelve to twenty-four hours later may be advantageous.

Intraspinal Treatment of Neurosyphilis with Standardized Salvarsanized Serum.—STONER (*Jour. Am. Med. Assn.*, 1917, lxviii, 610) concludes from his experience with the treatment of 72 cases of various forms of neurosyphilis that Ogilvie's modification of the Swift-Ellis method gives the most satisfactory results yet obtained, and with the minimum discomfort to the patient. By this method at least half of the patients have no discomfort at all, and most of the remainder have only trivial symptoms of transitory character. He says that with experience there is no greater risk in giving intraspinal treatment than intravenous. In none of the 72 cases was there evidence of untoward effects following treatments. The average number of spinal injections to a patient was four and the maximum, twelve. The spinal fluid leukocyte count was made normal in 40 per cent., the spinal Wassermann negative in 12 per cent., the globulin negative in 20 per cent., and the spinal fluid made entirely normal in 10 per cent. The spinal fluid improved in nearly 37 per cent., but remained unimproved in 13 per cent. Two-thirds of the patients were improved in one or more symptoms. It was found that clinical improvement did not necessarily parallel laboratory improvement. Paresis did not

show satisfactory results from the treatment, and the method did not seem of value in cases in which marked changes in the nervous structures had already taken place, as was to be expected. The author says that experience leads one to believe that intraspinal treatment cannot replace general treatment but must be used as an adjunct. He does not believe that intraspinal therapy is indicated in early neurosyphilitic involvements unless general treatment has failed. However, it is striking how much relief a single intraspinal treatment will give in early neurosyphilis when general treatment has failed. The author states that not all cases of neurosyphilis are amenable to treatment, but a surprisingly large percentage of patients were improved symptomatically and biologically if treatment is rationally and intensively employed.

PEDIATRICS

UNDER THE CHARGE OF

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The Place of Infant Welfare in Public Health Instruction.—KNOX (*Jour. Am. Med. Assn.*, vol. lxix, No. 14). "Eighteen per cent. of the total mortality of all ages occurs under one year. Infant mortality can be reduced by known methods, from one death within a year, to every five babies born (which is the rate in many portions of the country) to one death in every twenty babies born, which is the rate under satisfactory hygienic conditions, and which means the saving each year in the whole country of approximately 200,000 lives, a larger number than would be saved by the complete eradication of tuberculosis. If the capitalized value to the State of an infant life is, as has been claimed, $5000, the loss of wealth represented by this human wastage can be roughly estimated. It is to be emphasized, too, that babies that come healthfully through their first year look forward to a much longer life expectancy than do the cured patients from any illness. . . . In presenting the subject of infant welfare to students of hygiene, three distinct lines of approach should be followed. In the first place, infant welfare must be studied in relation to other branches of hygiene, of which it is an integral part. Therefore much that should be taught in a general curriculum of such a school requires no duplication in presenting the subject of infant welfare, except that the relation of the latter to the subject considered must be emphasized. For it is true that nothing is done in the community to improve health conditions in general which does not help the baby. Thus, for example, vital statistics, particularly birth registration, form the foundation of any infant welfare work. . . . The same can be said of general sanitation, housing, water supply, milk supply, and of industrial occupations and venereal disease in their relation to the health of the infant. . . . It would seem that infant welfare falls naturally into

two main divisions, one of which has to do with having better babies born. It presents as an ideal that every conception should result in a healthy baby. This leads at once to a discussion of the science of genetics and eugenics. . . . It would seem, however, that the reason for the prevention of the marriages of the notoriously unfit, and of the segregation or the unsexing of such persons, should be presented from the stand-point of the baby's welfare. Again, the effect of acute and chronic alcoholism, or of the abuse of other habit-forming drugs, in one or both parents, on the well-being of the child should be discussed from a thoroughly scientific point of view. The whole question of syphilis should be studied with special reference to stillbirths, premature births and lowered infant vitality. The effect of tuberculosis in parents on the vigor of offspring must be presented; likewise the effect of factory work, or hard manual occupation, on the part of the pregnant woman. Then, in connection with the obstetric department, steps should be taken to bring about more skilful aseptic obstetric practice. The question of training or abolishing midwives in this country, the early registering of expectant mothers at the obstetric clinics, thorough prenatal care, adequate obstetric service in rural districts, the establishment of obstetric substations under the control of health departments, these and similar subjects having to do with getting babies well-born are parts of infant welfare." The causes of infant illness and death during the first year may be divided into several groups: congenital debility and prematurity; digestive diseases; diseases of the respiratory tract; acute infections. Other points to be considered are (1) study of the milk supply; (2) maternal nursing; (3) housing conditions; (4) the income of the parents; (5) intelligent care on the part of the mothers.

Studies in the Nephritis of Children.—Hill (*Am. Jour. Dis. of Children*, October, 1917, xiv, No. 4). Dr. Hill discusses four methods of testing kidney function in children; viz., the added salt and urea test, the phenolsulphonephthalein test, the two-hour renal test, and the determination of the concentration of the urea-nitrogen in the blood. Of these tests the added salt and urea test is of little practical value in studying nephritis in children. The blood-urea determination is probably of slightly more value. The most valuable of the above-enumerated tests are the phenolsulphonephthalein and the two-hour renal tests. Their value lies in their simplicity and because of the reliable and important knowledge gained of the functional power of the kidneys. These two tests supplement each other, and give more valuable information when used together than can be gained from either when used alone. Their value does not lie so much in the matter of making the diagnosis, but they are valuable as guides to prognosis, which is usually rather difficult in the early years of life. The tests for function, when used together with a consideration of the general condition of the child, help greatly in making the prognosis. Repeatedly low functional tests, made at intervals of a few months, mean a poor prognosis. High phthalein excretion alone does not help in one way or another. High phthalein excretion, normal blood urea, and a normal response to the two-hour test warrant a conclusion that the process is a mild one, that the kidneys are only slightly damaged, and that there is a good chance for ultimate recovery.

OBSTETRICS

UNDER THE CHARGE OF

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Cholesterol in the Blood of Mother and Fetus.—SLEMONS and CURTIS (*Am. Jour. Obst.*, April, 1917) have studied the question as to whether the placental partition checks the interchange of fats between the maternal and fetal circulations. This is especially interesting in view of the fact that sometimes mothers who are disposed to be fat give birth to fat infants. Of late, however, quantitative determinations of the fat in mother and fetus yield very different results. In the blood of the mother at the conclusion of labor the amount of fat and fatty bodies may vary from 600 to 1200 mg. to 100 c.c. of blood; while in the blood of the fetus the quantity is from 500 to 700 mg. No indication has been found of equilibrium in the fat content of the two circulations. Beside fats which are composed of glycerin and fatty acids, there are other substances closely related to fats which are utilized in animal economy. They are lipoids, and cholesterol is one of them, of great physiological importance, and it is found in every cell. This substance in chemical structure is analogous to glycerin and like it combines with fatty acids. The writers undertook to study the blood of mother and fetus to determine the presence of cholesterol. During pregnancy the amount found in the blood of the mother varies considerably, and there is a notable increase during the latter half of gestation. It has been thought that this was produced by various organs in the mother's body, but there is no evidence that the placenta is a source of cholesterol nor can the adrenals or corpus luteum be proven to have a part in its production. The writers have obtained results indicating that cholesterol is transported through the placenta and that very probably the fetus is one of the causes for an increase in the cholesterol of the mother's blood. This excess begins about the fourth or fifth month of gestation when the fat metabolism of the fetus is most active, and this would naturally account for the increase of this substance in the mother's blood. Five cases were examined at the end of labor where delivery had been effected without anesthesia, and the total cholesterol of the mother's blood varied between 210 and 310 mg. In fetal blood the cholesterol was 115 to 225 mg. When delivery was conducted without anesthesia, none of the bodies formed from cholesterol were present in the fetal blood; in exceptional cases, as once where delivery had been effected by forceps under anesthesia, and in another where the mother had heart lesion and was delivered by Cesarean section under nitrous oxide anesthesia, the cholesterol bodies were found in fetal blood. When these bodies are absent from the blood of the fetus, the cholesterol is exclusively in the free form, and this is identical in both maternal and fetal blood. The employment of anesthesia frequently disturbs this relation, and the depth and duration of the anesthesia influence

the degree of disturbance. The absence of cholesterol bodies in fetal blood in normal cases indicates that they may not pass the placenta, while on the other hand, identical values for the free form in mother and child show us that cholesterol itself passes readily. So nearly alike are the quantities in the two circulations, that one cannot judge concerning the direction of its transportation. The interesting question arises as to whether cholesterol is a food or a waste product; at present the weight of evidence is in favor of the view that it is a waste product and that we should expect it to pass from the fetus to the mother. This would account for its increase in the blood of the mother, and for the excessive amounts found in the bile during pregnancy. This substance is colloid and the laws of its passage through the placenta are not those of diffusion. As the bile salts keep it in solution, it may naturally be supposed that the inorganic constituents of the placenta do the same thing. The calcium salts at the periphery of the chorionic villi may be connected with the transportation of cholesterol through the placental partition. In eclampsia the total cholesterol of the blood is increased but in cases where toxemia is produced, and failure in the action of the kidneys, the cholesterol is normal or diminished. In pernicious nausea cholesterol is not increased. The results of the writers' studies so far have been that in normal cases delivered without anesthesia, the difference between the total cholesterol of maternal and fetal blood is accounted for by the cholesterol bodies in maternal blood. In both maternal and fetal circulations the quantity of free cholesterol is the same. Free cholesterol can pass through the placental partition, but cholesterol bodies cannot. In auto-intoxication there is room for a practical application of the estimation of the quantity of cholesterol in the blood of the mother.

Retention of the Placenta Treated by Hydraulic Method.—Von Bassewitz (*Brazil-Medico*, Rio de Janeiro, January 20, 1917) describes his experience in securing expulsion of the placenta by Gabaston's method. Instead of using the crede or other manual method, the placenta is filled with saline solution injected through the umbilical cord. As the placenta becomes distended it usually stimulates uterine contractions while the fluid within the placenta and that which accumulates in the uterus help in its expulsion. When successful, this method acts very promptly. In the first of the two cases reported by the writer, the uterus seemed to have lost its tone almost entirely, but when saline fluid was injected from a can placed one and one-half meters (about five feet) above the level of the bed, vigorous uterine contractions occurred when 800 c.c. of salt solution had been infused. The placenta was spontaneously expelled in fifteen minutes. In the second case 4 liters of salt solution had been injected with apparently no result, and the obstetrician removed the placenta by the hand protected by a sterile glove. The patient had been delivered by forceps, and it was found that in the delivery the uterus had been drawn down to the vulva so that its contractive power had temporarily been suspended. This method is reasonably prompt and satisfactory where there is total retention of the placenta and complete atony of the uterus, and it should also prove exceedingly useful for those cases where the maternal and fetal tissues are unnaturally adherent.

DISEASES OF THE LARYNX AND CONTIGUOUS STRUCTURES

UNDER THE CHARGE OF

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Malposition of Cervical Vertebræ Simulating Osseous Tumor of the Rhinopharynx.—CYRIAX (*Jour. Laryngol., Rhinol. and Otol.*, August, 1917) describes the case of a female, aged twenty years, with poor resonance in singing, achings in the neck produced while practising with the violin, and with limitation in the rotary movement of the head to the left side. Dr. Dundas Grant discovered rhinoscopically a projection on the posterior tract of the upper pharynx, bony to digital pressure, which might be diagnosed as either a bony outgrowth, or as a forward displacement of cervical vertebræ. A skiagram revealed a rotation of the axis, with like displacements in decreasing ratio in the third, fourth and fifth vertebræ. The atlas appeared to be in normal position. At the request of Dr. Grant who had resected the nasal septum with some improvement in the vocal resonance, Dr. Cyriax treated the case by passive cervical adjustments, of which fifteen were practised during three weeks. Each procedure consisted of preliminary petrissage and stretching in order to induce relaxation of the cervical muscles and ligaments, followed by rotary movements in the direction of the limitation; the procedure consuming from eight to ten minutes. The treatment remedied the displacements, and after a subsequent adjustment of the axis some months later, the vertebræ remained in their proper alignment. The report is illustrated with reproductions of several skiagraphs before and after treatments, and with a number of photographic reproductions of vertebræ demonstrating the rotations which had taken place in the spine of the patient.

A New Instrument to Maintain a Dry Field in Tonsillectomy under General Anesthesia.—ISRAEL (*Laryngoscope*, February, 1917) describes and depicts his new appliance for this purpose. It consists of a pair of rubber tubings perforated at their distal ends which are passed along the floor of the nose into the pharynx, and which are attached anteriorly to a Y-shaped tube which is to be connected with any form of suction apparatus.

Hemiplegia following Tonsillectomy.—GRACEY (*Laryngoscope*, January, 1917) reports an instance in a boy, aged nineteen years, in which death supervened. SCRANTON (*Idem.*, February, 1917) reports another in a girl, aged eleven years, who recovered. The cause of the hemiplegia eluded detection in both cases.

Edema of the Glottis following Tonsillectomy.—MYERS (*Laryngoscope*, February, 1917) reports an instance in a physician, aged thirty-

five years. The epiglottis became turban-shaped, with infiltration of the glosso-epiglottic folds. Under applications of ice externally and by sucking, with occasional sprays of adrenalin solution, the condition subsided after some forty-eight hours.

Tonsillar Origin of Thrombophlebitis of the Cavernous Sinuses.— GOT (*Revue de laryngol., d'otol et de rhinol.*, July, 1917) reports in detail a case of phlegmonous tonsillitis with this sequence and describes the anatomical relations which may be regarded as the paths of transmission. He refers to two previously reported cases, all he could find in the literature, of which he gives succinct abstracts. All three were attended with suppurative thrombophlebitis of the ophthalmic veins and of the cavernous sinuses; and all three terminated fatally.

Cranial Osteomyelitis following upon Intranasal Operation for Frontal Sinusitis.—MACLAY (*Jour. Laryngol., Rhinol. and Otol.*, June, 1917) reports the record of a case of this kind, so far as he knows, the first to be published. A married woman, aged thirty years, had remained well for several years following extensive intranasal operations for removal of polypi from nose and maxillary antra, including submucous resection of the septum, curetting of the ethmoidal labyrinth, opening of the sphenoidal sinuses, and clearing of the frontal sinuses. She desired, however, riddance from annoying droppings of discharge into the throat which had persisted. Further intranasal operation was advised to improve the drainage from the frontal sinuses, and was readily performed with rasps under anesthesia. The frontal sinuses were washed out daily through a good-sized cannula for three days, during which everything appeared to go well. Then pain began at the root of the nose and inner angle of the left orbit with slight puffiness at the root of the nose. Despite such surgical interferences as seemed requisite things gradually got worse and death by coma ensued at the end of four weeks. An autopsy revealed a thick layer of pus under the dura covering the frontal lobes in their entirety and extending into the longitudinal fissure. The frontal bone was denuded of its pericranium for the most part and looked bleached. The nasal process of the frontal bone, the nasal bones, the nasal processes of the maxillæ, and the vertical plate of the ethmoid were involved in an inflammatory process of disintegration. Pus from the brain surface yielded the Staphylococcus albus and aureus and a streptococcus.

Cancer of the Esophagus Terminating in Fatal Hemorrhage from Ulceration into the Aorta.—DRONIN and CANUYB (*Revue de laryngol., d'otol et de rhinol.*, May 15, 1917) report in detail this case which has some peculiar features. It occurred in a man, aged forty-eight years, with inability to swallow culminating about one year after having accidentally swallowed a small quantity of caustic potash. Gastrostomy became necessary and afforded some mitigation, but on the fourth day after operation, death by asphyxia suddenly occurred during a copious hemorrhage from the air passages. Autopsy revealed a double perforation of the esophagus, one with the left bronchus and the other with the aorta.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Infectious Jaundice (Weil's Disease) and its Causative Micro-organism.—Infectious jaundice has been known in a great number of different districts as well as among peoples with different occupations. Its presence among soldiers, miners, and sewer-workers has been commented upon. In 1886 Weil described 4 cases with typical symptoms characterized by sudden onset, with fever and muscular pains, followed by jaundice and the appearance of bile pigment in the urine. The majority of cases showed evidence of a Bright's disease, and were accompanied by mucosal and subcutaneous hemorrhages. An endemic form of this disease has prevailed in Japan, and in 1916, INADA, ITO and others (*Jour. Exper. Med.*, 1916, xxiii, 377) reported the successful transmission of the disease to the guinea-pigs. The illness resulting in these animals resembled that in man, particularly in the appearance of jaundice, hemorrhages, and albuminuria. The experiments were conducted by inoculating blood from the patients directly into animals. Upon studying the blood, liver, and kidney of the guinea-pigs they discovered the presence of a spirochete which they named the Spirocheta icterohemorrhagiæ. It was furthermore found that the infection of animals can be accomplished by applying the virus to the unbroken skin. Similar results upon the transference of the disease from man to animals were accomplished by STOKES, RYLE and TYTLER (*Lancet*, 1917, i, 142) by the use of blood of British soldiers in Flanders who had Weil's disease. These authors also observed the presence of a spirochete resembling that isolated by Japanese workers. Subsequently the work in Europe was further confirmed by both French and British workers. Inada and Ito continued their work upon Weil's disease and showed that the serum of convalescent patients contained immune properties against the spirochete. In Japan the mortality in Weil's disease is high, averaging 38 per cent. On the other hand, the European disease has a mortality not exceeding 2 or 3 per cent. It was found that active immunity could also be induced in lower animals, but a passive immunity by injecting immune serum was not successful. In the districts where mine infection occurred it was more practicable to undertake disinfecting of the ground and removal of contaminated material than to actively immunize the laborers. An interesting finding was made by the Japanese authors in the demonstration of an identical

spirochete in rats. ITO and HOKI (*Jour. Exper. Med.*, 1917, xxvi, 341) have since shown that the rat is an active carrier of Spirocheta icterohemorrhagiæ and that the animal suffers from this infection as a natural disease. The microörganism was found to be located in the kidney and was excreted with the urine. Subsequently, NOGUCHI (*Jour. Exper. Med.*, 1917, xxv, 755) also found a similar spirochete in the wild rats of New York. He cultivated this microörganism as well as the Japanese and European strains. By means of immune reactions he was able to show that these spirochetes from different quarters of the globe were identical. Noguchi, however, points out that this microorganism is not a true spirochete, nor is it of the nature of a spirillum, so that he offers a name for the new genius, Leptospira. KANEKO and OKUDA (*Jour. Exper. Med.*, 1917, xxvi, 325) had an opportunity of studying 43 autopsies of Weil's disease. The ages varied from two to seventy-three; there were 36 males and 7 females. The spirochetes were found present in the blood during the first stage of the disease and became abundant in the kidneys in the second stage when jaundice was marked. At this time they were also found in the liver and adrenal. The mortality is highest during the second stage. It is difficult to indicate why the mortality in Japan is so much higher than in Europe. Noguchi suggests that the Japanese strain has already acquired a marked increase in virulence to human subjects, owing to a more frequent passage from man to man. This is, of course, assuming that the natural habitat of the microörganism is in the rat. An interesting controversy arises in regard to this new spirochete in that the organism previously described by Kaneko as the causative agent in rat-bite fever appears to be identical with the one under discussion. There appears no question that infectious jaundice in recent years has been more prevalent than we have previously known it.

Experimental Nephritis Due to Bacillus Mucosus Capsulatus.— The influence of infections, acute and chronic, in the production of nephritis, particularly of the glomerular type, is becoming more and more felt as the evidence accumulates from autopsy room, experimental laboratory, and bedside. MAJOR having reported previously (*Jour. Med. Res.*, 1917, xxxv, 349) his success in producing glomerulonephritis by repeated intravenous injections of Staphylococcus aureus toxins in rabbits which had been given a preliminary injection of uranium nitrate, now reports (*Idem.*, 1917, xxxvii, 125) the production of similar lesions resulting from the intravenous use of B. mucosus capsulatus. This work was also done on rabbits. A single large injection, the growth on a twenty-four-hour agar slant, washed off in 5 c.c. of sterile salt solution, was sufficient to cause an acute hemorrhagic nephritis in six hours. The glomeruli were obscured by a mass of erythrocytes, and fibrin thrombi were seen in their capillaries. The tubules showed marked necrosis and desquamation, and contained granular and hyalin casts. By reducing the dosage and giving it repeatedly over a long period, Major was able to produce the pictures of subacute and chronic nephritis. In the former there was a slight proliferation of connective tissue and a few fibrotic glomeruli, but the striking change consisted in the degeneration of tubular epithelium. In the latter the kidney under the capsule presented a granular surface and the microscopic picture was that of

diffuse chronic nephritis, showing numerous areas of round-cell infiltration and fibrosis, especially of the glomeruli. The author quotes from literature concerning the pathogenicity of B. mucosus capsulatus that it has been found in chronic nasal sinus infections, in an epidemic of coryza, and from kidney abscesses. In fourteen control rabbits he found no cases of so-called "spontaneous nephritis."

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Experimental Typhus Fever in Guinea-pigs. — NEILL (*Public Health Reports*, July 13, 1917, xxxii, No. 28) describes certain gross and histological lesions in the genitals of male guinea-pigs showing the characteristic temperature reaction induced by the intraperitoneal injection of virulent typhus blood. These are contrasted with the lesions produced in guinea-pigs by Rocky Mountain spotted fever, with the conclusion that the pathology of the two diseases in the guinea-pig presents a very similar picture, so far as the essential nature of the lesions is concerned. In well-developed male guinea-pigs, which had been intraperitoneally injected with the Mexican typhus virus, the following changes have been observed: From nine to fifteen days after inoculation, the temperature of the animal becomes elevated to from 40.5° to 41.0° C., and if the scrotum, with the testicles in place, be examined, a definite swelling is observed. If the skin be of a light color, some redness may be noted. These external changes subside in a few days. If the animal be killed when the fever and scrotal changes are at their height, dissection reveals the following gross findings: The skin of the scrotum looks apparently normal, but if it be carefully dissected from the tissues immediately beneath, definite hemorrhages appear in the cremasteric fascia, just external to the parietal laminæ of the tunica vaginalis. If these structures be incised and the testicle and epididymis exposed, hemorrhages of a similar nature will be noted immediately beneath the visceral laminæ of the tunica vaginalis. The extent of these hemorrhages varies from a few minute petechiæ to nearly complete envelopment of the testicles by hemorrhagic areas. If the animal be examined at the height of the process, i. e., one or two days after the swelling is first noted, the lesions above described are indistinguishable in their gross appearances from the lesions of Rocky Mountain spotted fever at the same stage of development of the disease, that is, one or two days after the swelling of the scrotum is first noted. In the spotted

fever animals, in contradistinction to the typhus animals, the disease becomes progressively more severe. Hemorrhages into the skin of the scrotum take place, and in some cases typical necroses of the scrotum, paws, and ear tips are observed before the death of the animal, which usually follows. On the other hand, the lesions of typhus fever rapidly clear up and soon the animal is as well as ever. After citing the literature (Ricketts, Lecount, Wolbach) on the pathology of Rocky Mountain spotted fever and mentioning certain descriptions of the histopathology of the exanthem in typhus fever (Frankel, Aschoff, Poindecker) attention is directed to the apparent resemblance of the essential vascular lesions described in the two diseases. The author reports that the histopathology of the lesions in the male genitalia of guinea-pigs is essentially similar in the two diseases, at the same stage of development, and also resembles the descriptions in the literature of the pathology of typhus fever and Rocky Mountain spotted fever in the human species. The minute lesions described for typhus fever guinea-pigs consisted of degenerative and proliferative changes in the smaller bloodvessels with perivascular exudation consisting chiefly of endothelial leukocytes and cells of the lymphocyte series. Neil summarizes the work as follows: Definite gross and minute pathological changes in the genitals of male guinea-pigs reacting to Mexican typhus virus have been described. (1) The gross lesions occurred in about 70 per cent. of such animals examined. (2) These depend upon lesions of the bloodvessels. (3) The lesions are similar in process but milder in character than those occurring in guinea-pigs infected with Rocky Mountain spotted fever.

Are Schoolrooms Drier than Deserts? — PALMER (*Am. Society of Heating and Ventilating Engineers*, Chicago, July, 1917) states that schoolrooms admittedly dry and drying do not appear to be as dangerous to health as deserts. This assertion is based on a familiarity with many schoolrooms in the Northeastern States and a perusal of the accounts of desert conditions in the works of geographers and travellers. Warm, dry schoolrooms have without doubt been the cause of many headaches, lowered vitality, colds and inattentiveness, but even so, the results do not seem as severe as the effect of desert air. Two citations will illustrate this: Huntington (1915) states that "In such a place as Death Valley in summer, with the thermometer at 100° to 135° in the shade, it is almost impossible to drink enough water to preserve normal physiological conditions. Even a brief period of physical activity gives rise to much discomfort, and people who stay through the summer are in danger of suffering permanent injury to health." Macfie (1909) observes that a "Too dry climate, or rather a climate with too great drying capacity, seems in time to have an exhaustive effect on the European constitution. The extreme summer heat of the African desert is certainly most enervating and there can be little doubt that many lives have been lost by a compulsory summer sojourn on the South African Karroo." Schoolroom air may and does contain less moisture during much of the winter season, than desert air. Schoolroom air has as low or lower relative humidity than desert air. Schoolroom air does not extract as much moisture from wet objects nor from the human body as desert air. On the basis of their dehydrating power schoolroom air is not dryer than the air of deserts.

An Epidemic of Septic Sore Throat Due to Milk.—HENIKA and THOMPSON (*Jour. Am. Med. Assn.*, May 5, 1917, lxviii, No. 18, 1307) studied an explosive outbreak of 325 cases of septic sore throat in a community of 941 people directly traceable to an infected milk supply, which occurred in Galesville, Wisconsin, from February 26 to March 19, 1917. They state that the interesting factors in this epidemic were: The virulence of the infection; the tracing of the source of infection to six cows; the possibility of the cows becoming infected from the milker; the large number of family infected; the small number of contact cases; the short period of incubation, and the abrupt checking of the epidemic. They went to Galesville at the height of the epidemic, recognized the organism causing the disease, traced the source of infection to a single dairy, isolated the infected cows from the herd, and had the satisfaction of seeing the epidemic checked. It is believed that the issuing of the bulletin, requesting the citizens to boil all milk and water and giving full directions for disinfecting all discharges from the patients, and such other precautions as were necessary to prevent contact infections, checked the epidemic, and was a large factor in preventing contact cases. This is a measure that could well be adopted in all milk-borne and water-borne epidemics. This epidemic furnishes additional proof that pasteurization of bottled milk under official supervision is the only method of securing a safe milk supply. Rosenow and Hesse (*Jour. Am. Med. Assn.*, May 5, 1917) studied the same epidemic, and state that the clinical picture in this epidemic was typical of "septic sore throat" as described in numerous other milk-borne epidemics. Etiological relationship of the streptococcus found in the milk was proved. The disease occurred almost exclusively in persons who consumed the milk. In some instances the drinking of one glass was sufficient to bring on an attack. The streptococcus was found in enormous numbers in the material from mastitis quarters of the cows' udders and in small numbers in a normal quarter. It was also isolated in large numbers from the throats of patients. High virulence of the streptococcus was proved by inoculation of animals. The lesions produced resembled those found in patients, especially in those animals in which the methods of inoculation simulated those which occurred in the epidemic. Erysipelas was produced in a monkey by scratching the skin with a wire dipped in the infected material. In the same monkey inflammation of the throat associated with acute enlargement of the lymph glands in the neck, with surrounding edema and otitis media followed swabbing the throat with cotton saturated with the same material. Peritonitis, pericarditis, endocarditis, myocarditis and synovitis were common in the animals as in patients. Heating the milk to 60° F. for twenty minutes was sufficient to render it innocuous. Virulent bacteria may be present in the udder of cows with no demonstrable sign of the disease. It is practically impossible to handle milk without risk of contamination from human and other sources, even though the rigid technic of an operating room be employed. Since milk is such an excellent culture medium, inspection of dairies, certification and grading of milk according to sediment tests and bacterial counts as now practised, while valuable, cannot permanently safeguard the public health. Efficient pasteurization should be universally adopted.

WAR MEDICINE

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THE PROBLEM OF DEALING WITH VENEREAL DISEASES IN GREAT BRITAIN.

BY COLONEL T. H. GOODWIN.

FOR some years past the problem of venereal diseases and their serious effects on the British nation have been occupying the earnest attention of the medical profession in England.

The problem is one of magnitude and importance; it is difficult, except in the case of the Navy and Army, to obtain reliable statistics regarding these diseases, but the following estimates may, I think, be accepted as approximately correct:

The Royal Commission on Venereal Diseases estimated that in the larger towns in England at least 10 per cent. of the total number of inhabitants were infected with syphilis, while gonorrhea was even more prevalent. This would mean that in London alone there were 450,000 syphilitics. Erb estimated that 12 per cent. of the population of Berlin was syphilitic and that over 70 per cent. of the population had, at one time or other, contracted gonorrhea. Fournier estimated that 15 per cent. of the inhabitants of Paris were syphilitic.

As regards syphilis, Sir William Osler places this disease as third on the list of what he terms the "killing diseases," and so generally are the inroads of this disease manifested on every tissue of the body that Sir William graphically remarks that "a medical student who is thoroughly grounded in this disease and the affections to which it gives rise would have acquired a good knowledge of all branches of his profession."

The question naturally occurs to us as to why when such diseases

as typhus, typhoid, scarlet fever, epidemic diarrhea and others, have been adequately grappled with by the Public Health Service (or Department of State Medicine), yet venereal diseases would appear to have pursued their ravages, if not unchecked, at least inadequately dealt with. The answer I think is simple. It is due to the mistaken policy of silence, the unwillingness to recognize the existence and importance of venereal disease, the national habit of—as regards these diseases— "hiding our head in the sand." It was not until last year that the State made serious effort in England to control and combat these diseases.

As regards the Army, with which I have been intimately connected for nearly twenty-five years, in spite of the fact that the best methods of treatment are in vogue and that the incidence of the disease has been diminishing, we find that in 1912 the average number of men incapacitated or "off the strength" was 593, which, with an army of 107,000 men, represented a loss of over 216,000 working days in the year.

I say that the incidence of the disease in the Army has been diminishing; this is the case, and is still continuing to be the case. The rate for the year 1913 was 5.3 per cent. per annum, whereas the rate for last year was 2.1 per cent. per annum; but we must not allow ourselves to be misled by these figures into the adoption of what might be a too optomistic view. We should bear in mind that, while active service conditions prevail, the subject of venereal disease can be more adequately dealt with than during times of peace.

I think, however, that we are justified in believing that improved methods of educating the soldier in this matter, the provision of greater facilities as regards games and recreations in cantonments, and the decrease of alcoholism have had a very considerable effect in decreasing the incidence of venereal disease. What have been the chief errors and shortcomings in the past which have acted as obstacles to progress as regards prevention of venereal diseases?

I think we may summarize them as follows:

1. The policy of silence and concealment and the consequent lamentable lack of education and diffusion of knowledge on the subject.

2. The inadequate facilities for diagnosis and treatment.

3. The absence of any provision for compulsory notification.

4. The neglect to prevent quacks from treating the disease.

5. The fact that the transmission of venereal disease to another person by a person who is knowingly infected does not constitute a legal crime.

How are these factors now being dealt with?

1. EDUCATION. The National Council for combating venereal disease, inaugurated in November, 1914, while the Royal Commission was pursuing its investigations, has done much and is doing much excellent work.

This Council, with Lord Sydenham as President, embraces many leaders of the medical profession and has also—and to this I would direct special attention—representatives of the churches and of many women, social and philanthropic workers, in close coöperation. The aims of the Council are briefly as follows:

(a) Provision for education and enlightenment.

(b) Provision of greater facilities for treatment.

(c) Provision of increased opportunities for study of these diseases on the part of medical practitioners and students.

(*d*) Promotion of legislative, social, and administrative reforms.

As regards the Army alone, up to June last year over 600,000 soldiers had attended the lectures given with the approval of the Director General, Army Medical Service, in military centers.

2. DIAGNOSIS AND TREATMENT. The facilities for these in the past have been grossly inadequate.

As regards early detection of venereal disease, it is probable that in England it is only in the Navy and Army that really full advantage is taken of the more modern methods. As regards facilities for modern methods of treatment, there has also been a lamentable lack of provision.

The policy of the Royal Commission has been that of rendering the best means, both of diagnosis and treatment, available, free of charge, to every venereal patient who is willing to take advantage of them. The point of view taken is that venereal disease once acquired, it is both the duty and the interest of the State to see that it is promptly cured.

Outlines of the Scheme. Facilities for *diagnosis* are organized, so far as possible, in connection with existing laboratories in universities and in general and county hospitals. To these laboratories material is sent for examination.

As regards *treatment.* Wards in general hospitals for indoor treatment are allocated to venereal patients.

For outdoor patients evening clinics are provided. The objection to the provision of special hospitals for these diseases lies in the resulting publicity.

The wards and clinics should be accessible to all medical men and medical students who are desirous of acquiring proficiency.

It is recommended that salvarsan should be provided gratuitously, under proper safeguards, to private practitioners for use among the poorer patients.

3. COMPULSORY NOTIFICATIONS. Logically, compulsory notification and compulsory treatment would appear to be sound, but it is perhaps doubtful if they would be practicable measures.

Sir Malcolm Morris himself believes that, under present conditions, these measures are out of the question, and that notification would deter patients from seeking proper treatment, and that the inclination of patients to place themselves in the hands of quacks would become more serious than ever.

Sir William Osler would welcome notification, but there are many others who, looking at the matter from the point of view of the individual patient, would regard his confidence as inviolable.

The conclusion of the Royal Commission was against compulsory notification.

Personally, I believe that, with the advance of education and enlightenment and the recognition by the public of the gravity of the matter, notification will become compulsory.

4. SUPPRESSION OF QUACKERY. The commission emphatically recommends that all advertisements of remedies for venereal diseases should be prohibited.

The commission was also in favor of the legal prohibition of treatment, by unqualified persons, of these diseases, but apparently there are some practical difficulties in securing the operation of such a law at present.

I am not versed in legal matters, but to my mind such prohibition would be an essential and most important measure, and my personal opinion is that unauthorized treatment of these diseases should constitute a penal offence.

I also think that it should be the duty of a medical man to acquaint the parents of any girl who contemplates marriage with a man whom he is treating for venereal disease, and that such a communication should be recognized as privileged.

5. The Wilful Communication of Venereal Diseases. This should, in my humble opinion, constitute a legal crime. The proof of knowledge might be difficult, but the effect of such a legal measure could only, I think, tend toward the good of the community.

Gentlemen, time is limited and the above is simply a brief sketch of how the question stands—so far as I am aware—in England at the present day.

The present world-wide war is, so far as we can see at present, productive of nothing but evil, but it seems possible that, in the post-war future, benefits to the race may result.

The war is teaching us to regard life and death as less important matters than the future welfare of mankind, and if such matters as adequate control of venereal diseases, world-wide prohibition of alcohol and an increasing instead of a decreasing birth-rate result, it may possibly be found that the war, terrible as it is, was not without some good results.

Survey of Army Food.—The food division of the Surgeon-General's Office has undertaken to conduct nutritional surveys in as many camps as possible, and as often as time will permit. The survey party will in each instance consist of four commissioned officers and a number of enlisted men of the Medical Department. The commissioned officers will for the most part be scientists who have had experience in food chemistry, food sanitation, or physiology. They will in each camp inspect the food with special regard to its nutritive value, but will also gather information concerning the character, quantity, and source of each food, the amount of waste, and the analysis of the garbage. From the collected data they will be in a position to make recommendation concerning dietaries and nutritional matters in general.

The need of such study is evidenced by the numerous reports of nutritional troubles in the European armies. Scruvy has not been uncommon, as reports from Mesopotamia and Italy prove, and there is evidence that even where no definite nutritional disturbance has developed the healing of wounds has been delayed by poor nutritional condition. Digestive disorders have been common and at times serious and it is to the credit of our Surgeon-General's Office that active measures are being early taken to prevent such troubles in our own forces.   O. H. P. P.

General Orders Concerning Care of Soldiers' Feet and Regulations for Training Officers and Enlisted Men in Orthopedics.—General Orders 133 give evidence of the care and forethought which the Government is showing concerning the important matter of orthopedics.

It is ordered that medical officers in medical officers' training camps

must receive as a minimum three hours' instruction in this work and more time if available.

For those officers who elect orthopedic service there will be given courses of intensive instruction in various universities similar to the intensive courses being given in other branches.

The line officers and candidates for a commission are also to receive instruction in the care of the feet and its coverings, and also elementary instruction concerning body posture and joint injuries.

Enlisted men will receive at least one hour's practical instruction along the same lines once a month, and the enlisted men of the medical department will get fuller instruction.

Furthermore, it is planned to have particular attention directed by the medical officers to the condition of the feet of the enlisted personnel at each regular semimonthly physical examination, and treatment will be instituted in all necessary cases. Discharge from the service will not be recommended until a reasonable amount of treatment has been given by the orthopedic surgeon on duty.   O. H. P. P.

Report of Conference Committee on Red Cross Nursing Problems Appointed by the Chairman of the War Council.—Released for Publication October 1.—One of the important problems presenting themselves in connection with the medical preparation for the war has been the question of an adequate supply of satisfactory nurses. Accurate statistics of available nurses were not obtainable and the usual variations of conditions in the different States added to the difficulty. The number of registered nurses and Red Cross nurses could readily be ascertained, but it was impossible to estimate the sufficiency of the remainder for civilian nursing if a large percentage of the former classes were called away for military purposes. Furthermore, it was obvious that the total supply would promptly become inadequate if a demand such as might readily be anticipated should develop.

At a recent meeting on Red Cross nursing problems held in Washington at which representatives of all the National organizations and members of the Medical Advisory Committee and Red Cross Committee on Coöperation were present, the general plan of enrollment of nurses as carried out by the National Committee on Red Cross Nursing Service was approved with certain modifications. These are as follows:

1. The lower age limit for Red Cross nurses is reduced from twenty-five to twenty-one years. The upper limit is left indefinite, to be dealt with separately in each case.

2. The requirements governing training schools are modified so as to qualify for Red Cross enrollment the graduates of schools which are recommended by State Boards of Registration as giving courses sufficiently thorough to prepare nurses for Red Cross service. This eliminates the former requirement that Red Cross nurses must be graduates of schools having a daily average of 50 patients. It is estimated that approximately 500 training schools may thus be added to the acceptable list, whenever it may be desirable, owing to war shortages of nurses, to ask the State Boards for recommendations.

3. In order to further increase the supply of nurses, the schools giving a three-year course are to be requested to advance the date of graduation of pupil nurses, perhaps to the end of their second year of study, should the exigencies of war make such action seem desirable.

4. It is recommended that in addition to the steps already taken to supply volunteer nurses' aides, which the Committee approves, the period of practical hospital experience for these volunteers be increased to one month of eight hours' service each day under the supervision of the Red Cross, and that the Red Cross volunteer aids be used for service in our own country, and that women under twenty-one years shall not be selected. In view of the provision already made for the instruction of volunteer aids in connection with base hospitals and the large number of women who have completed the course of theoretical instruction and whose names are on file, the Committee believes that the immediate extension of this service is not pressing, but approves of the authorization of civil hospitals to give this information to nurses' aids as needed, subject to approval and under direction of the Red Cross. It is further recommended that only those hospitals approved by State Boards of Registration of Nurses shall be so authorized.

There can be no doubt of the importance and value of this branch of the Red Cross Committee's work and the outlined plans should certainly meet all requirements for the present. It should, however, be pointed out in connection with (4) that in some instances the former custom of a three months' course of four hours a day will not only give a greater total of hours but will be more convenient to both the aids and the hospitals. O. H. P. P.

United States Medical People with Foreign Forces.—There are 3180 medical officers, nurses, and members of ambulance sections of the United States Army now attached to the British and French forces. This total is made up of 870 medical officers and 470 nurses with the British forces and 40 ambulance sections, each of 46 officers and men (a total of 1840), with the French Army.

A Study of Reëducation of Disabled Soldiers in France and England. —By LINSLY R. WILLIAMS, M.D.—Through the courtesy of the Vice-Chairman of the National Research Council of the Council of National Defence, permission has been granted to review Dr. Williams's report.

This study of conditions in both France and England deals in great detail with all questions touching upon the reëducation of disabled soldiers and sailors, the organization of military orthopedic hospitals, the special schools of reëducation, the manufacture and settling of artificial limbs, and the reëducation of the blind. In many ways the methods employed in the two countries are similar, and from this exhaustive study Dr. Williams has drawn conclusions which cannot fail to be of inestimable value to our country. These conclusions are presented in the form of a suggested program for the United States, and these may be quoted verbatim:

1. All permanently disabled from wounds or sickness be transferred from France to United States cantonments to a central hospital.

2. Central hospital should have staff of experts of highest order in neurology, psychiatry, heart disease (functional and organic), ophthalmology, orthopedic surgeons, surgeons, medical men, and other specialists. Also employers of labor and representatives of labor unions.

3. Special hospitals should be established for neurology, psychiatry, orthopedic surgery, heart disease, and limbless.

4. Workshops should be operated in conjunction with this hospital.

5. Patients should be transferred as rapidly as possible to these special hospitals, where workshops should be established giving wide latitude in the selection of work.

6. A special school should be established for the blind.

7. Employment committees of a permanent nature should be organized in many localities.

8. Hospitals and workshops should be near the East Coast until the increased number of wounded demands new hospitals in other populous centers.

9. The work organized should be placed on a permanent basis and buildings should be considered from this point of view.

10. New technical schools will have to be established.

11. The interest and sympathy of the public should be obtained by nation-wide publicity.

12. A large staff and considerable funds will be needed to carry out any satisfactory program.

The importance of this problem may be realized when it is brought home that 6 per cent. of all wounded become permanently disabled. A varying percentage of these are able to return to their former occupation, but many are liable to pauperism if not given technical educacation. Apparently the men do not always take willingly to this education, for Germany requires them to stay in the army until the education is complete, and England uses moral suasion plus 5 shillings extra a week as an added inducement. Often the men mistakenly believe that they will lose their pensions if they learn a trade and become self-supporting.

In France there are eighteen main military orthopedic hospitals, each completely equipped and having associated with it a reëducation school. These schools give such training as carpentry and joinery, machinery, tinsmith and forge, manufacture of toys, tailor shops, bookbinding, commercial courses, etc., and in some instances there are also agricultural schools giving instruction in farming, gardening, and raising poultry or live stock. At the completion of the training employment is secured, but there is no follow-up system.

The blind in France are transferred to schools maintained by private funds, but the War Department pays in part for maintenance. There are approximately 3000 blind soldiers and sailors in France, and about one-half of these are receiving education in such branches as massage, carpentry, cooperage, glass polishing, mat and brush making, basket making, typewriting and reading from Braille type. Employment is secured but the follow-up work is still inadequate.

In England the methods and organization are in general the same. The military orthopedic hospitals which have been established by the War Department are under the direction of Robert Jones, the most prominent orthopedic surgeon in Great Britain. All cases needing orthopedic treatment are transferred to these hospitals, and there is a special hospital to which all men who have lost one or more limbs are sent to have the stumps prepared for receiving an artificial limb.

Each hospital has its associated workshop, and at the earliest possible moment patients begin some form of manual work. If possible the man returns to his previous occupation, but if not he is taught a new trade, in the choosing of which he is allowed considerable latitude. All of the artificial limbs are made on the premises, and before the

patient leaves the hospital the efficiency and satisfaction of the artificial limb must be certified to by the patient, the maker, the surgeon, and the commanding officer.

Three weeks before it is thought that a patient will be ready to leave, an application for discharge and pension is sent in, so that his pension is available when he leaves the hospital. At present a man who is totally disabled receives a minimum weekly pension of 27 shillings, 6 pence and an additional 5 shillings weekly for the first child, 4 shillings, 2 pence for the second and 3 shillings, 4 pence for the third. Pensions in cases of partial disability are based upon the degree of the disability, and a corresponding percentage of the total disability pension is awarded.

The blind are treated in England much as in France, but the number of cases seem to have been much less, and a more satisfactory follow-up system has been possible.

Such a brief abstract as this cannot do more than suggest the great amount of detailed information contained in the original report which it is to be hoped will soon be made available by publication.

One further point which is repeatedly emphasized in this report is the importance of the relation which the whole problem of the reëducation of the disabled bears to the labor situation. The men must be taught trades in which they can obtain employment, nor must these trades be allowed to become too crowded and conditions disturbed. Labor and trade unions must be considered and a representative of these unions should be on every committee concerned with such problems. Experience has taught that it is only by correlating all phases of the question and by full coöperation under a central authority that the best results have been obtained.   O. H. P. P.

Disinfection of Drinking Water.—DAKIN and DUNHAM (*British Med. Jour.*, May 26, 1917) state that bleaching powder or similar hypochlorite or chlorine preparation has been used with the greatest success for the sterilization of relatively large volumes of drinking water when troops are practically stationary. The problem of sterilizing small individual quantities of water, such as are needed by cavalry or rapidly moving troops, is much more difficult. For such purposes the instability of small tablets containing the minute quantity of active disinfectant required led the writers to make a number of experiments. The first experiment was made with chloramine-T. It was unsatisfactory. If waters were heavily contaminated and hard and alkaline the concentration required was too great, though this could be reduced by use of citric, tartaric, and other organic acids. The next attempt was with preformed toluene-sulphondichloramines, and first results were encouraging; but when put up in tablet form too much time was required for solution to bring about prompt sterilization. Greater solubility and stability were obtained with p-sulphondichloraminobenzoic acid. This can be prepared from cheap, readily available material. The formula is $Cl_2N.O_2S.C_6H_4COOH$. The presence of the COOH group confers a slight but definite solubility in water, which is increased by dispensing it with alkaline salts, such as sodium carbonate, sodium bicarbonate, borax, etc. The writers propose for convenience that the designation "halazone" be used for this substance. Tests of the efficacy of this "halazone," both in powder and tablet form, were

made, using tap water and B. coli; hard water and feces suspension; hard water and 10 per cent. city sewage; tap water and 5 per cent. city sewage; hard water and B. coli. The "halazone" was in varying degrees of concentration, as 1 to 250,000, 1 to 500,000, 1 to 1,000,000. The ordinary routine was to take 5 to 10 drops of the treated water, place on agar to count surviving organisms, and use suitable controls. The experiments appeared to show that in a concentration of 1 to 300,000 an ordinarily heavily contaminated water was sterilized in thirty minutes. This concentration could be relied on to remove coli, typhoid, or cholera organisms. A convenient formula for tablets weighing 100 to 105 mg. is: sulphondichloraminobenzoic acid, 4 per cent.; sodium carbonate, 4 per cent. (or dried borax 8 per cent.); pure sodium chloride, 92 per cent. Grind the acid with dry salt and then add the sodium carbonate. Pass mixture through a 40-mesh sieve. No lubricant or other addition is necessary. Tablets must be stored in small amber-colored bottles. One tablet prepared as above sterilizes 1 liter of moderately contaminated water. If contamination is excessive, use two tablets to 1 liter or quart. Sufficient time has not yet elapsed for final reports on the stability of the tablets, but under ordinary conditions no decomposition was noted after two months. Bright sunlight acting on tablets in clear glass bottles did cause decomposition. The estimated cost in England of disinfecting water by the use of "halazone" is 2 cents per 100 gallons of water.   M. J. R.

Note on the Prevention of Pediculosis.—GUNN (*British Med. Jour.*, May 5, 1917) gives very favorable reports on the use of thin undershirts made of muslin (so cheap that the original intention was to throw them away after using once) soaked in the following solution: naphthalene and sulphur, each, 1½ ounces; benzol or gasoline, 1 gallon. No inconvenience results from the use of undergarments so treated. The effect on pediculi is not immediate. The writer quotes from a letter from France in which it was stated that 200 dead pediculi were counted on a shirt that had been treated with the above solution. The solution has been applied under a plaster cast without irritation to the skin.
                                                                    M. J. R.

Vincent's Angina.—CAMPBELL and DYAS (*Jour. Am. Med. Assn.*, June 2, 1917, lxviii, No. 22, 1596) state that Vincent's angina was formerly comparatively rare. It seems to have first become prevalent in France, where it was known as trench mouth. Now it is so prevalent that it may be classed as among the commonest of disabilities among the troops. Usually the condition is not such as to confine the patient to bed, but the depression and inability to masticate properly cause a serious lowering in efficiency. Vincent's angina is an infectious disease of the mucous membrane of the mouth, throat, bronchi, and prepuce. By far the most frequent site of infection is the mouth and throat. Next in frequency are the bronchial cases. The preputial cases are rare. The largest percentage of cases are of the tonsillar type. Characteristic symptoms of this type are a yellowish-gray membrane, fetid breath, some pain on swallowing, and enlarged and tender cervical lymph glands. Absence of headache, myalgia, and marked prostration distinguish it from diphtheria and acute tonsillitis.

There is sometimes a slight febrile reaction, which is often absent. The pulse and respiration are but slightly elevated. The next most frequent type is a deep ulcer on the ramus of the lower jaw behind the last molar tooth. In untreated cases, infection spreads along the margin of the gums, causing pyorrhea. Pyorrhea caused by Vincent's organisms is also frequent. In an otherwise healthy mouth it is at first limited to the region of the incisors. General infection of the mouth is the severest type of all, and the patient is acutely ill. The membrane extends over the cheeks, tongue, fauces, pharynx, and palate and even to the lips. Deep ulcers may also develop. The authors found a few Vincent's organisms in about 50 per cent. of all swabs taken by them from the throats of troops at Bramshott. In early cases the bacilli are usually more numerous than the spirochetes, but in more advanced cases the spirochetes are usually the predominant organisms. The organisms are best stained with carbol-gentian violet. Both spirochetes and bacilli are usually Gram-negative. The organisms can be grown anaërobically in ascitic broth containing a piece of tissue. The incubation period of the disease is unknown. Diphtheria and Vincent's angina may coexist. The combination is rare, but patients with Vincent's angina when in contact with a Klebs-Loeffler bacillus carrier may readily become infected. Patients giving a syphilitic history, especially when undergoing mercurial treatment, favor the development of Vincent's angina. Some of the severest cases are found in syphilitics. A healing ulcer about the mouth and throat closely resembles a syphilitic mucous patch. Treatment consists in local applications of arsenic, iodin, silver nitrate, trichloracetic acid, hydrogen peroxide, tincture of ferric chloride, or potassium permanganate. In slight lesions any of these will bring about a cure. Arsenic, however, especially in the form of salvarsan, is undoubtedly the most useful remedy. The authors found that local applications of liquor arsenicalis (Fowler's solution) swabbed on three or four times a day was most effective.   M. J. R.

Permanent Interallied Commission for the Purpose of Examining Questions of Interest to War Cripples.—The minutes have come to hand from the Surgeon-General's office, through Major E. G. Brackett, of the first two meetings of the Permanent Interallied Commission for the purpose of examining questions of interest to war cripples. An outgrowth of the Interallied Commission for Professional Reëducation of War Cripples, and formed as a result of the suggestion of the earlier body this permanent commission, has announced the following outline of its purposes: (1) To second by all means in its power the efforts of the national institutions, public or private, to improve the situation of the cripples of war. (2) To collect and keep up to date the most complete information possible in regard to all problems interesting to these cripples. (3) To publish an interallied periodical bulletin. This publication, *Les Mutiles de la Guerre*, is to appear monthly or bimonthly, and is also to be solely devoted to the same interest. It is to be under the management of a committee which will include a specialist for each of the principal groups of questions to be dealt with in accordance with the program of the Assembly, viz.: Functional reëducation; prosthesis and orthopedy; professional reëducation; blind,

deaf, and those suffering from lesions of the nervous system. The moral, economic, family, and social interests of the invalids of war. Comparative legislation and regulations: At the second meeting a plan was approved for the creation of an interallied institution for research, experiments, and the collection of documentary evidence concerning mutilated and disabled soldiers. This institution would comprise the following: (a) Research laboratories where a special study would be made, both from a psychical and physiological point of view, of the best means of utilizing in a rational manner those mutilated in the war. (b) Workshops for study, construction, and experiments regarding: (1) Prosthesis; (2) special instruments; (3) apparratus for the protection or support of mutilated soldiers. (c) A permanent museum of artificial apparatus or examples of practical work and plans executed in different countries. (d) A library comprising books, plans, articles, and documents of every kind concerning disabled soldiers. All persons interested in work in connection with disabled soldiers would have free access to this institute. The *Interallied Review* would be the official journal of this institution and would acquaint the general public with its researches and discoveries. The joint services of the institution and the *Review* would permit the translation and communication to all inquirers of documents of interest regarding disabled soldiers. The institution would not cease to exist with the conclusion of peace, but would then take up all questions relating to victims of accidents at work. The personnel of the commission includes representatives from each of the allies at war. The United States and Japan were not represented at the first meetings, but it is assumed that subcommittees will be (or perhaps have been) appointed to coöperate with the interallied commission in this work. Surely there is no problem of greater importance, and the vastness of the need is well indicated by the extensive machine which it has been deemed necessary to put into action and by the prominence of the personnel involved.

La Pratique de l'Hygiéne en Campagne.—By A. Tournade. Pp. 222. Paris: L. Fournier, 1916.—The present war has brought out small manuals on military hygiene by French, English, and American authors. The most striking feature of all these is the very marked difference between them and works on military hygiene of even a dozen years ago. Today a good part of the space is occupied by a consideration of personal hygiene, excreta disposal, the sterilization of water, the control of flies, lice, and rats and immunization against infectious disease.

In the present volume great emphasis is laid on personal cleanliness and arrangements for shower baths, and other baths are described. One shower is figured as consisting of two barrels, an open kettle over a fire, a small pump, and a piece of perforated pipe. Another specially constructed, but simple and portable, apparatus is described. Much attention is given to "delousing," and perhaps the reader is confused by the number of insecticides given. Sulphur fumigation is recommended for outside clothing. The details are given for delousing a large number of men at one time as well as for cleansing patients on admission to a hospital. For the destruction of rats the author has the

greatest confidence in chemical poisons, though he also recommends Danysz's virus. The rats are to be attracted to one place by liberal feeding for several days and then suddenly a plentiful supply of poisoned food is provided.

The disposal of feces is a most important matter. For a more or less permanent encampment a shallow straddle trench is recommended. The construction of trench privies is also described in detail. They are placed in short detours excavated out of the trenches and so arranged that water cannot flow back into the trench. The material is covered with earth and frequently disinfected. All forms of excreta disposal must be continuously supervised by a special squad detailed for the purpose. Another method of disposal recommended consists of a shallow portable trough, about seven feet long and eighteen inches wide, which is kept filled with a disinfectant solution. The lower end of the trough is over a cess-pit, and twice a day a plug is pulled out to allow the contents to flow into the pit.

Vaccination is considered the most important factor in the prevention of the infectious diseases, and it appears to be obligatory in the French Army not only for smallpox and typhoid fever but for both the paratyphoids. The vaccines may be used separately or combined. Tunard strongly advocates vaccination against cholera.

For disinfection the author seems to rely too much on fumigation, with formaldehyde spray or even with sulphur dioxide, and not enough on thorough washing and the use of steam. For the isolation of scarlet fever he would inclose the bed with gauze and disinfect the throat of the patient and anoint the skin with eucalyptus oil according to the method of Milne, a method which has received scant approval in other countries. When enemy territory is captured all occupied places are to be thoroughly disinfected and all prisoners promptly freed from vermin and carefully examined before they are sent back from the front.

The book is, to a considerable extent, made up of abstracts from general orders, which perhaps accounts for its not very logical arrangement. It is interesting at many points as showing the ingenuity of the French in meeting the many difficult problems which confronted them at the opening of the war, but on the whole it does not seem to be such an up-to-date exposition of medical science as similar pocket manuals by Lelean and Vedder.   C. V. C.

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